

Cadralazine Kinetics

Case Study

- How to create a one-compartment model
- How to write equations for the noncompartmental parameters
- How to obtain initial parameter estimates
- How to fit your model to your data
- How to use Notes to keep track of your modeling work
- How to define alternative one-compartment model parameterizations

This page is intentionally left blank

Cadrilazine Kinetics: A One-Compartment Model

Prerequisites

The prerequisite for this case study is having worked through the SAAM II introductory tutorial, “Getting Started with SAAM II Compartmental.”

What you will learn in this case study

- How to create a one-compartment model using the model building tools.
- How to create a bolus experiment on the model using the experiment building tools where the amount of the dose is entered in the data file.
- How to enter (working with) data.
- How to create experimental samples and associate them with data.
- How to write the noncompartmental parameters.
- How to obtain initial parameter estimates for your model parameters.
- How to solve your model and view the solution.
- How to fit your model to your data, and view the statistical information associated with the “Fit,” including derived variables (noncompartmental parameters).
- How to use Notes to keep track of your modeling work.
- How to define alternative one-compartment model parameterizations.

Data Required

The data file for this case study is

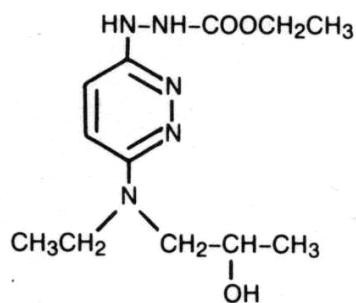
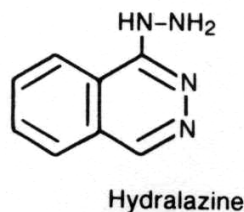
cadrilazine.dat

This data file is a text file. The contents of this file are included at the end of this case study.

Introduction

This case study will reinforce how you perform the basic operations in the SAAM II Compartmental application.

The model used in this case study was developed to describe cadralazine pharmacokinetics based on analysis of plasma concentrations that were measured after injecting an intravenous (iv) dose of this drug. Cadralazine is an antihypertensive drug that acts as a peripheral arteriolar vasodilator.¹ It is chemically similar to hydralazine except that it has a protected hydrazine group. As a result, it does not appear to cause the systemic lupus erythematosus-like syndrome that occurs in some patients who are treated with hydralazine.

**Cadralazine****Hydralazine**

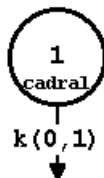
Cadralazine dosing is normally by the oral route in amounts of 15 to 30 mg daily, often in combination with other drugs. Cadralazine is metabolized to a small extent in the liver with most being excreted in the urine. The plasma half-life is 0.8 to 3.2 hours.

The data for this case study were taken from Wakefield et al.² This is a theoretical paper in which population modeling techniques are discussed. Cadralazine was used as an example because the drug decays monoexponentially following an iv injection. The experiment performed was to inject a single dose of 30 mg into each subject, and to take serial samples from plasma at various times. Wakefield et al. reported results from ten patients and we will use the data from one patient in this case study.

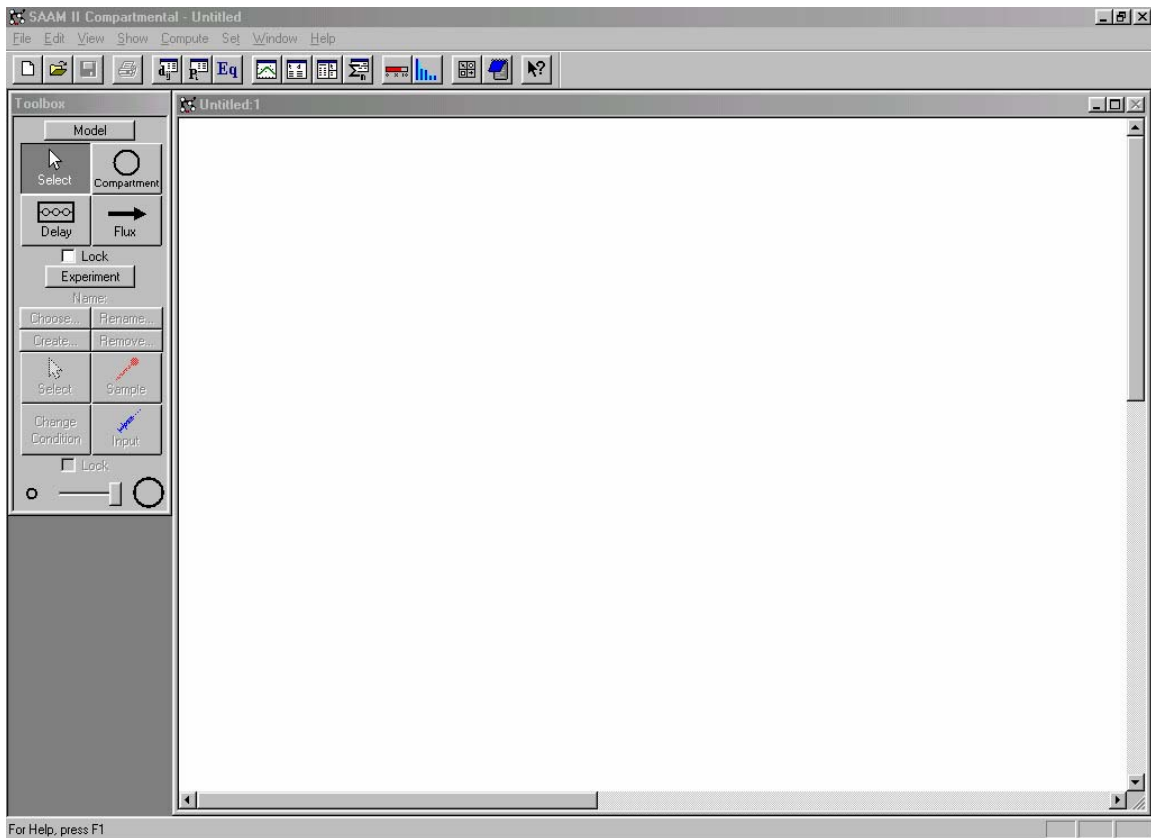
1. McTavish, D., Young, R.A., Clissold, S.P. "Cadralazine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of hypertension." *Drugs* 1990; 40:543-60.
2. Wakefield, J.C., Smith, A. F. M., Racine-Poon, A., Gelfand, A. E. "Bayesian analysis of linear and non-linear population models by using the Gibbs Sampler." *App Statist* 1994;43:201-21.

Part 1. Create a one-compartment model using the SAAM II Compartmental application.

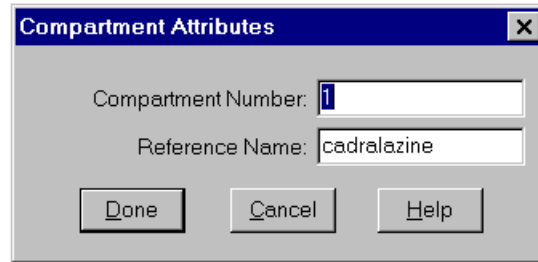
This part of the case study will show you how to create the following one-compartment model in the **SAAM II Compartmental** application:



1. **Start** the **SAAM II Compartmental** application. The **SAAM II Compartmental** main window will open as follows:

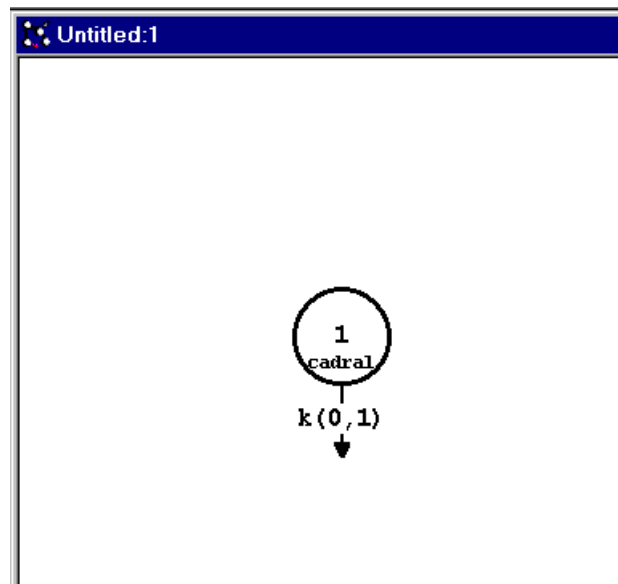


2. Create a one-compartment model.
 - a. In the **SAAM II Toolbox**, click **Model**.
 - b. In the **SAAM II Toolbox**, click **Compartment** (this tool is now available).
 - c. Click on the **Drawing Canvas** approximately where you would like the compartment to be located. Notice as you move the cursor on the **Drawing Canvas** that the cursor has a small compartment associated with it to indicate that the **Compartment** tool is available. A compartment with the number **1** will appear on the drawing canvas.
 - d. Double-click **Compartment 1** to open the **Compartment Attributes** dialog box.
 - e. Type “cadralazine” in the **Reference Name** box. The **Compartment Attributes** box will appear as follows:



- f. Click **Done**.
3. Construct a loss from **Compartment 1**.
 - a. In the **SAAM II Toolbox**, click **Flux**.
 - b. Click on **Compartment 1**, and then click anywhere on the **Drawing Canvas**.
 - c. This will create a loss, $k(0,1)$, from **Compartment 1**. No matter where you click on the drawing canvas, the loss will always point down.

Your **Drawing Canvas** will appear (in part) as shown below:

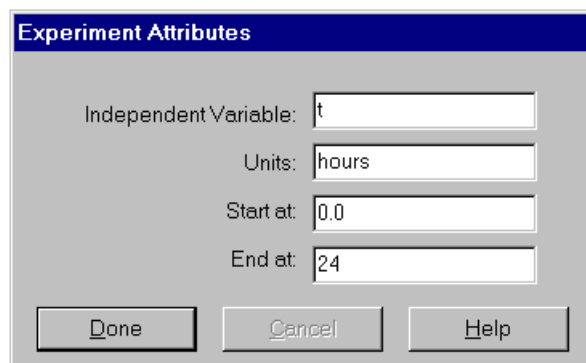


At this point, you have successfully created a one-compartment model with a single loss from **Compartment 1**. Now you need to reproduce the experiment performed in the laboratory on this model.

Part 2. Create the pharmacokinetic experiment on the model.

1. Create the experiment.

- a. In the **SAAM II Toolbox**, click **Experiment**. Notice that the **Model** tools are unavailable and the **Experiment** tools are available. The **Experiment Attributes** dialog box will open.
- b. Change the entry in the **Units** box from “minutes” to “hours.”
- c. Enter “24” in the **End at** box. The **Experiment Attributes** dialog box will appear as follows:



- d. Click **Done**.

The **Create Experiment** dialog box will appear on the **Drawing Canvas**. The choice of experiment **Types** is an **Experiment** or a **System**. **Experiment** is selected with the name “Exper”. Replace “Exper” with “Cadralazine” by typing “Cadralazine” in the **New Name** box. The **Create Experiment** dialog box will appear as follows:



- e. Click **Create**.




Experiment vs. System. The **Create Experiment** dialog box is where you create your experiment. There are two types of experiments - “Experiment” and “System”.

The **Experiment** type will invoke SAAM II's differential equation machinery. When you create this type of experiment, your compartmental model will be interpreted by SAAM II as a system of differential equations. Once parameter values and inputs have been specified, SAAM II can Solve the system of differential equations, and can Fit your model to your data. This type of experiment is designed to deal with time dependent data following an experimental (exogenous) input into the system.

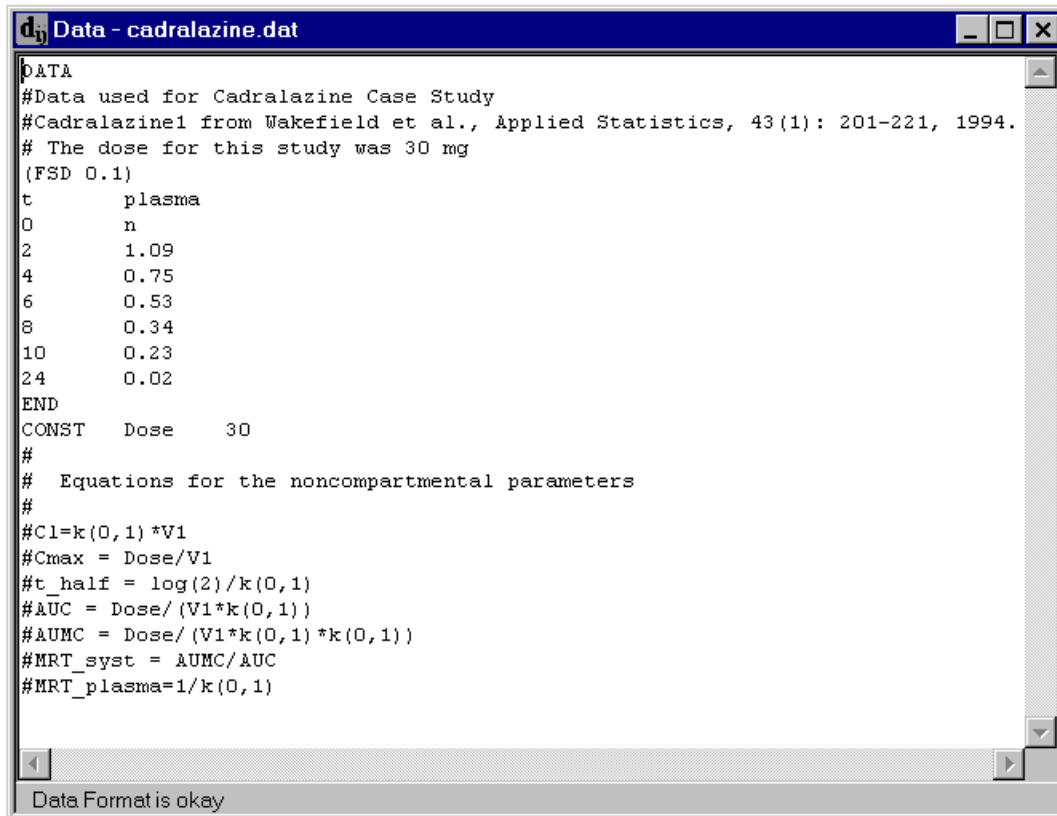
The **System** experiment creates a system of algebraic equations whose coefficients are the $k(i,j)$ of your compartmental model. The System model is used primarily in tracer-tracee experiments to describe the tracee data in the steady-state.

The default **New Name** is "Exper". This can be changed to a name of your choice. The name you enter will appear just below **Experiment** in the **SAAM II Toolbox** as shown below.



2. Add the data to your model.
 - a. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data** . The **Data** window will open.

- b. In the **File** menu, click **Open**. The file **cadralazine.dat** should appear in the list (if it does not, find the folder where you put this data file).
- c. Double-click **cadralazine.dat**. The data in this file will appear in the **Data** window as follows:



```

DATA
#Data used for Cadralazine Case Study
#Cadralazine1 from Wakefield et al., Applied Statistics, 43(1): 201-221, 1994.
# The dose for this study was 30 mg
(FSD 0.1)
t      plasma
0      n
2      1.09
4      0.75
6      0.53
8      0.34
10     0.23
24     0.02
END
CONST  Dose    30
#
#  Equations for the noncompartmental parameters
#
#C1=k(0,1)*V1
#Cmax = Dose/V1
#t_half = log(2)/k(0,1)
#AUC = Dose/(V1*k(0,1))
#AUMC = Dose/(V1*k(0,1)*k(0,1))
#MRT_syst = AUMC/AUC
#MRT_plasma=1/k(0,1)

```

Data Format is okay




Entering constants in a Data file. You will notice in the data file, following the END statement, the line “CONST Dose 30”. You can enter constants in your model such as doses, weights, heights, etc. using the CONST operator. Constants, so designated, must lie outside a data stream, i.e. streams between DATA and END. This particular case will be used to illustrate experimental inputs defined using constants thus making it convenient to store this information in several study files.

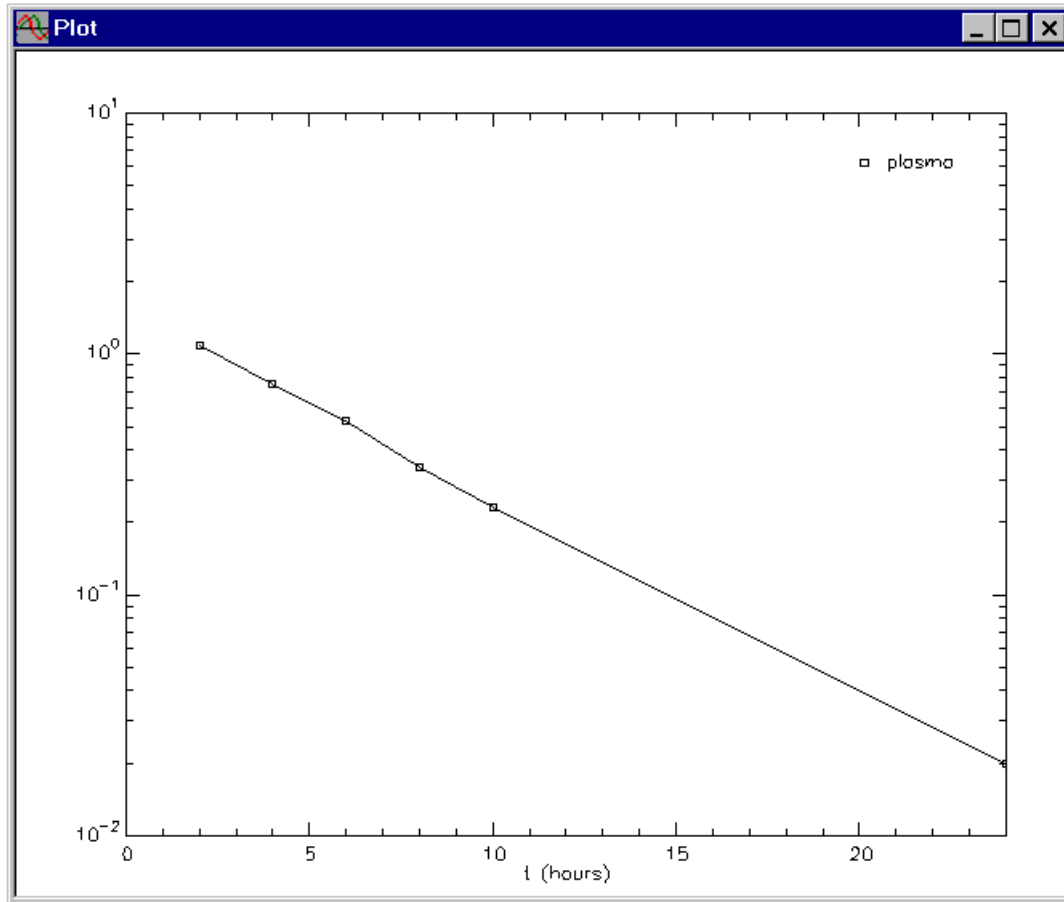


Entering comments in a Data file. You can enter comments in your data file if you precede each line with “#.” In this data file, comments are provided which explain where the data came from. In addition, the equations for the

noncompartmental parameters are entered as comments. This is for convenience; later in the case study, these will be pasted into the **Equations** window.



- d. Close the **Data** window.
3. View your data using a line plot.
 - a. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . The **Plot and Table Variables** dialog box will open.
 - b. Be sure the **List All Variables** check box is selected. (Click this box if it is not selected).
 - c. Click **plasma** to move it to the **Current Selection** pane.
 - d. Click **Done**. A plot of the data will appear in the **Plot** window.
 - e. In the **View** menu, click **Line Plot**.
 - f. In the **View** menu, click **Semilog**. Your plot will appear as follows:



g. Close the **Plot** window.

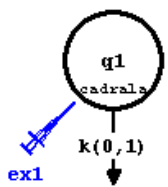


Line Plots. The data can be viewed as a linear or semilog plot after they have been loaded into the SAAM II **Data** window. When plotted as a semilog plot, they can help you decide how many exponentials (compartments) will be needed for the model. In this case, because the data appear as a straight line in a semilog plot, it is clear that a single compartment will be sufficient.



4. Add the appropriate experimental input to the model. In this subject, a bolus input of 30 mg of cadralazine was administered intravenously.
 - a. In the **SAAM II Toolbox**, click **Input**.
 - b. Click Compartment **q1**, and then click on the **Drawing Canvas**. An input arrow, **ex1**, will appear on the drawing canvas pointing to Compartment **q1**.
 - c. Double-click **ex1**. The **Exogenous Input** dialog box will open.

- d. In the **Input Type** pane, select **Equation**.
- e. In the **Equation** box, type “ex1=Dose”.
- f. In the **Event Start** box, enter “0”.
- g. In the **Event Stop** box, enter “0”.
- h. Click **Add**. The model with the **Exogenous Input** dialog box will appear on the **Drawing Canvas** as follows:



Exogenous Input

Name: Reference Name: Units:

Type	Initial	Constant	Start	Stop	Repeat Every	Nr. Repeats
Equation	ex1 = Dose		0.000	0.000	-	-

Input Type:

Bolus
 Infusion
 Primed Infusion
 Equation

Initial Amount:
 Constant Rate:
 Event Start:
 Event Stop:
 Repeat Every:
 Nr. of Repeats:

Equation:

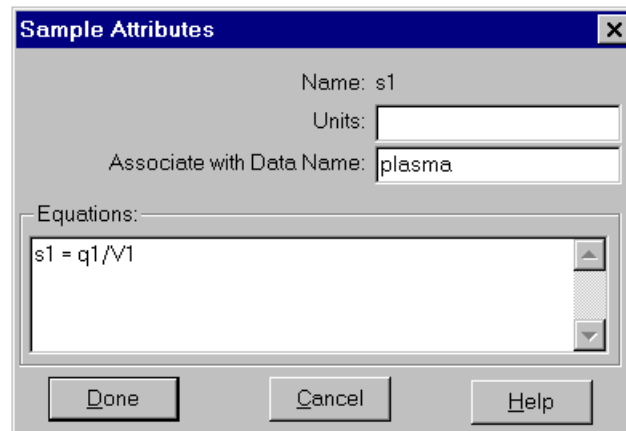
- i. Click **Done**.



Specifying a bolus injection using an equation. Remember you have entered information on the amount of the bolus injection as a constant in your data file. To specify this as a bolus in the **Exogenous Input** dialog box, you write the information in equation format. This is what links “Dose” with **ex1**. Since the dose is administered as a bolus, the event start and stop times are zero.



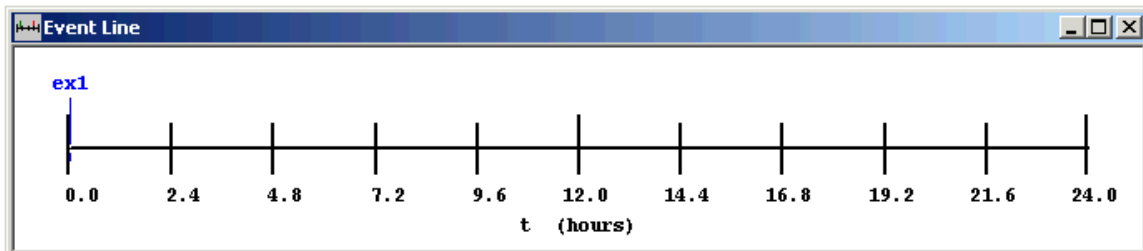
5. Create a sample. This sample represents the measurements you collected in your actual experiment.
 - a. In the **SAAM II Toolbox**, click **Sample**.
 - b. Click Compartment **q1**, and then click on the **Drawing Canvas**.
 - c. Double-click **s1** to open the **Sample Attributes** dialog box.
 - d. In the **Associate with Data Name** box, type “plasma”.
 - e. In the **Equations** box, edit the sample equation “ $s1=q1$ ” to read “ $s1=q1/V1$ ”.
The **Sample Attributes** dialog box will appear as shown below:



- f. Click **Done**.
6. View the Event Line.

It is useful to have a visual representation of your experiment in terms of when experimental inputs were done, and when samples were taken. This can be observed using the Event Line.

- a. In the **Show** menu, click **Event Line**. The **Event Line** will appear as follows:



The **Event Line** shows both the times of the test input(s) and samples. In general, you can leave the **Event Line** open if you wish.

- b. Close the **Event Line**.

Part 3. Defining Derived Variables (Noncompartmental parameters).

The parameters for your model are the rate constant $k(0,1)$ and the volume $V1$. The rate constant $k(0,1)$ is a fractional measure of the elimination rate of the drug, and it has units of inverse time (in this case, 1/hour).

Usually, it is of interest to calculate the elimination clearance of a drug. This is defined, for a one-compartment model, as the product of the elimination rate constant and the distribution volume of the compartment. In other words

$$Cl = k(0,1) * V1$$


In the language of SAAM II, clearance Cl is called a derived variable as it is a function of the model parameters $k(0,1)$ and $V1$. As you recall, parameters are variables that appear in the equations characterizing the model or experiment, but were not given numerical values. SAAM II automatically determines the model parameters. In addition, SAAM II can calculate values for functions of the model parameters. These are called derived variables. Following a successful "Fit," both appear in the **Statistics** window in the **Parameter/Variable** pane.

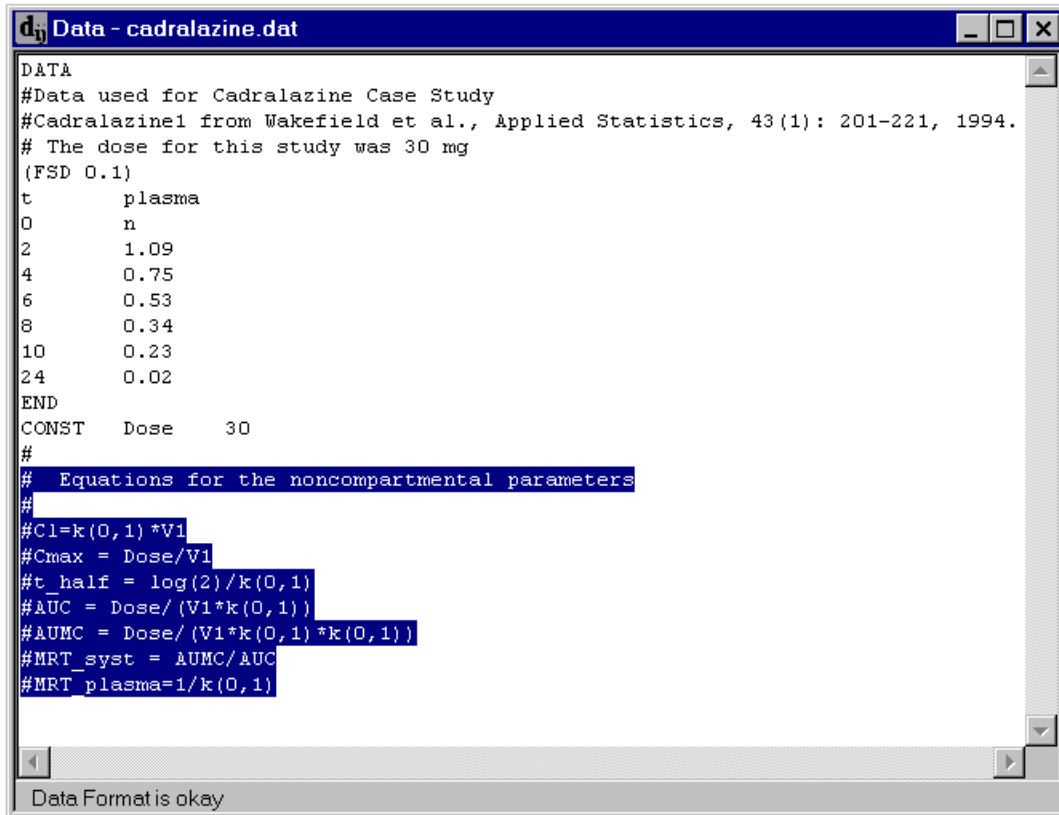
Besides clearance, there are a number of other noncompartmental pharmacokinetic parameters that can be estimated using the one-compartment model. These are

$$\begin{aligned} Cl &= k(0,1) * V1 \\ C_{max} &= Dose / V1 \\ t_{half} &= \log(2) / k(0,1) \\ AUC &= Dose / (V1 * k(0,1)) \\ AUMC &= Dose / (V1 * k(0,1) * k(0,1)) \\ MRT_{syst} &= AUMC / AUC \\ MRT_{plasma} &= 1 / k(0,1) \\ V_{ss} &= Cl * MRT_{syst} \end{aligned}$$

Notice that in this list there are two mean residence times. One is the system mean residence time (MRT_{syst}); this is the average time a drug particle remains in the system before being irreversibly lost. The other is the plasma mean residence time (MRT_{plasma}). This is the average time the drug stays in plasma before being irreversibly lost. Since this is a one-compartment model, the two are the same.

You can enter these parameters directly. For convenience, they can be cut and pasted from the **Data** file to the **Equations** dialog box as described below:

1. In the **Show** menu, click **Data**, or alternatively, on the **SAAM II Toolbar**, click **Data** . The **Data** window will open.
2. Select and copy the equations for the noncompartmental parameters. The selected information will appear in the **Data** window as follows:




```

DATA
#Data used for Cadralazine Case Study
#Cadralazine1 from Wakefield et al., Applied Statistics, 43(1): 201-221, 1994.
# The dose for this study was 30 mg
(FSD 0.1)
t      plasma
0      n
2      1.09
4      0.75
6      0.53
8      0.34
10     0.23
24     0.02
END
CONST  Dose    30
#
# Equations for the noncompartmental parameters
#
#C1=k(0,1)*V1
#Cmax = Dose/V1
#t_half = log(2)/k(0,1)
#AUC = Dose/(V1*k(0,1))
#AUMC = Dose/(V1*k(0,1)*k(0,1))
#MRT_sys = AUMC/AUC
#MRT_plasma=1/k(0,1)

```

Data Format is okay

3. Close the **Data** window.
4. In the **Show** menu, click **Equations**, or alternatively, on the **SAAM II Toolbar**, click **Equations** . The **Equations** dialog box will open.
5. Paste the equations in the **Equations Defined Here** pane in the **Equations** dialog box.
6. Remove the “#” from the beginning of each equation. The **Equations** dialog box will appear as follows:

```
Eq Equations
Equations Defined Elsewhere (read-only):
flux(0,1) = k(0,1) * q1
ex1.bolus = 0.0
ex1.infusion = 0.0
s1 = q1/V1

Equations Defined Here:
# Equations for the noncompartmental parameters
#
C1=k(0,1)*V1
Cmax = Dose/V1
t_half = log(2)/k(0,1)
AUC = Dose/(V1*k(0,1))
AUMC = Dose/(V1*k(0,1)*k(0,1))
MRT_sys = AUMC/AUC
MRT_plasma=1/k(0,1)
```



Equation syntax. There are two points to remember about equation syntax in SAAM II. First, while it may be appealing to define half-life (half-life and half-time can be used interchangeably) as $t_{1/2}$, this is improper syntax, and SAAM II will display an error message. The other point is that the natural log is “log,” not “ln.” If you define, for example, $t_{\text{half}} = \ln(2)/k(0,2)$, “ln(2)” will be interpreted as a parameter instead of an algebraic operation, and appear as a parameter in the **Parameters** dialog box.



- To view the differential equation generated by SAAM II, in the **View** menu, click **Diff. Eq.** The **Equations** dialog box will appear as follows:

```

Eq Equations
-----
Equations Defined Elsewhere (read-only):
flux(0,1) = k(0,1) * q1
ex1.bolus = 0.0
ex1.infusion = 0.0
s1 = q1/V1
q1' = - k(0,1)*q1 + ex1

Equations Defined Here:
# Equations for the noncompartmental parameters
#
C1=k(0,1)*V1
Cmax = Dose/V1
t_half = log(2)/k(0,1)
AUC = Dose/(V1*k(0,1))
AUMC = Dose/(V1*k(0,1)*k(0,1))
MRT_syst = AUMC/AUC
MRT_plasma=1/k(0,1)

```

8. Close the **Equations** dialog box.

Part 4. Obtain and enter the parameter values

Before you can Solve (simulate) your model or Fit your model to your data, you must provide numerical estimates for the parameters of your model. These are the parameters that appear in the **Parameters** dialog box.


The parameters for your model are the rate constant $k(0,1)$ and the volume $V1$.

1. Enter parameter values.



Initial parameter estimates. How the initial estimates for the parameters $k(0,1)$ and $V1$ were obtained is explained in the appendix for this case study. Initial estimates for both the iv bolus and iv constant infusion into the single compartment model are discussed. How the estimates are obtained applies to any experiment in which you are using a single compartment, or monoexponential model to analyze data following an iv bolus or constant infusion.



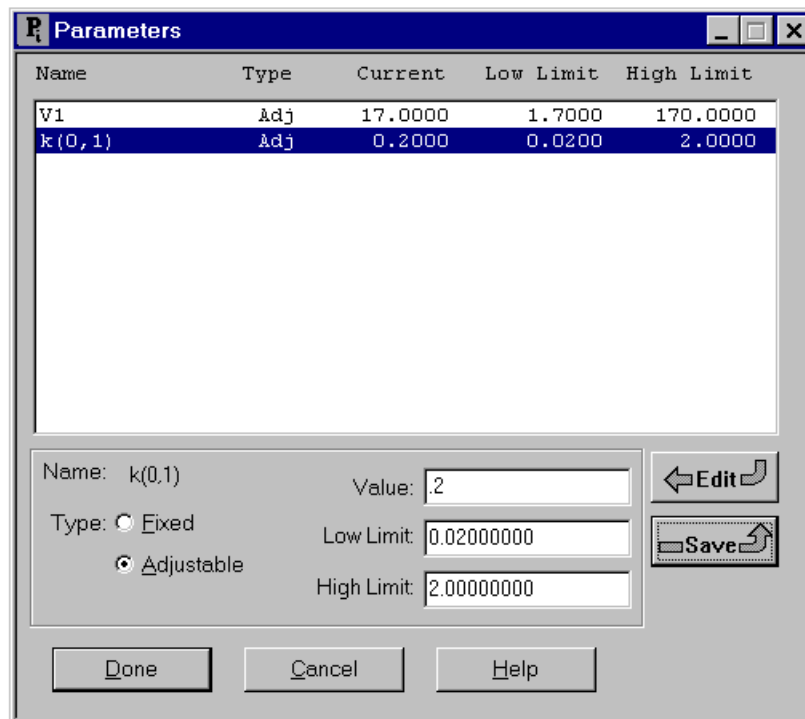
- a. In the **Show** menu, click **Parameters**, or alternatively, on the **SAAM II Toolbar**, click **Parameters** . The **Parameters** dialog box will open.

If $k(0,1)$ is not selected, double-click $k(0,1)$ to select it. Be sure the **Adjustable** option is selected.

- b. Enter “0.2” in the **Value** box, and click **Save**.

The current value of $k(0,1)$ will appear as “0.2;” the low and high limits will automatically be set equal to “0.02” and “2.0” respectively.

- c. Double-click $V1$ to select it.
- d. Enter “17” in the **Value** box, and click **Save**. Your **Parameters** dialog box should appear as follows:



- e. Click **Done**.

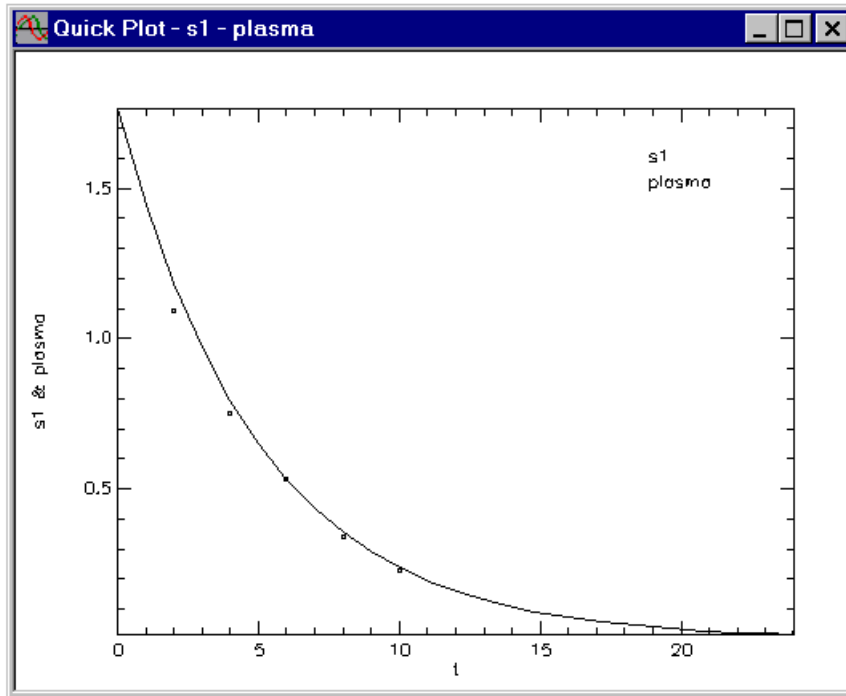
Part 5. Solve the model, fit the model to the data, and view the solution.

1. Solve your model.

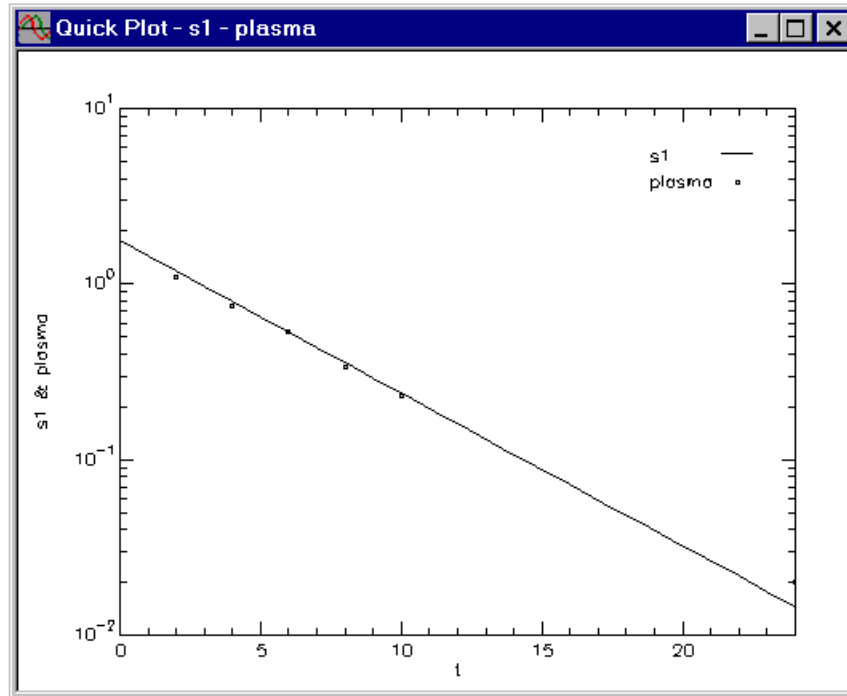
In the **Compute** menu, click **Solve**, or alternatively, on the **SAAM II Toolbar**,


click **Solve** .

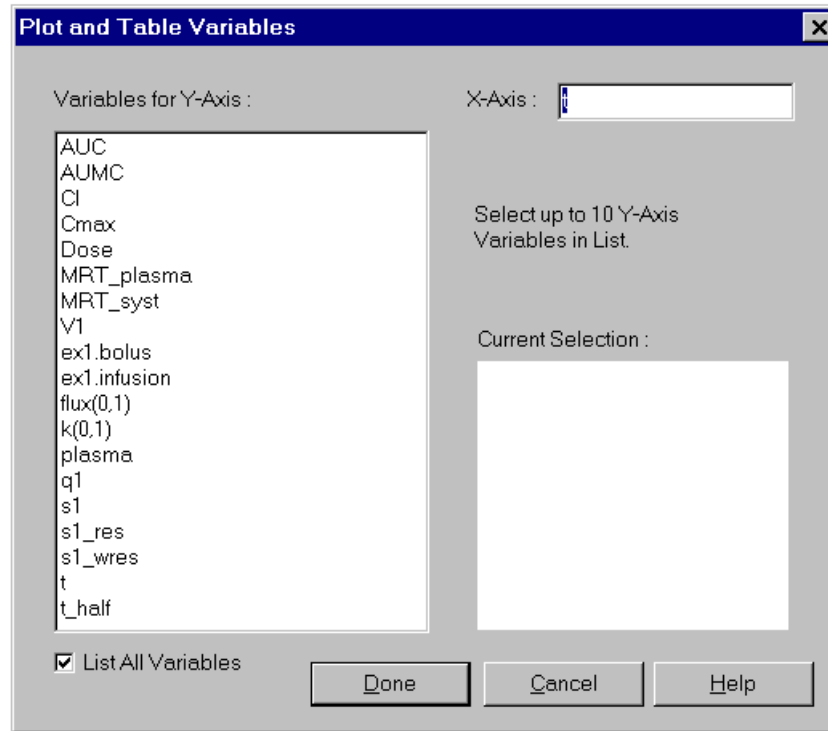
2. View the solution to your model using **Quick Plot**.
 - a. Click **s1** on your model to select it.
 - b. In the **View** menu, click **Quick Plot**, or alternatively press **Ctrl** and **M** simultaneously. The following plot will appear on in the **Quick Plot** window. Notice the scale is linear.



- c. To view this plot with a semilog scale, in the **View** menu, click **Semilog**. The following plot will appear as follows:

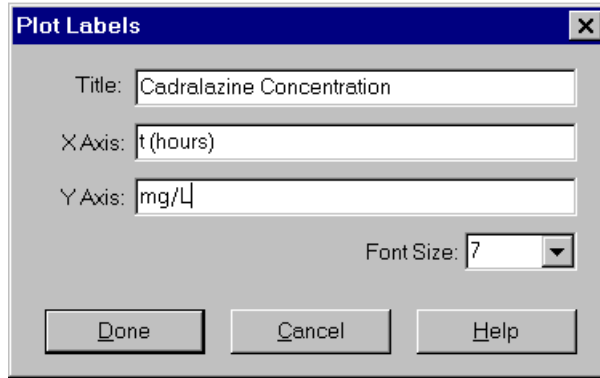


- d. Close the **Quick Plot** window.
3. View the solution to your model using the **Plot** command.
 - a. In the **Show** menu, click **Plot**, or alternatively, on the **SAAM II Toolbar**, click **Plot** . If the **Plot** window opens with a previous plot, in the **Set** menu, click **Plot/Table Variables** to open the **Plot and Table Variables** dialog box. If this dialog box does not open as follows, check the **List All Variables** check box:



You can now choose from the different variables for the Y-Axis for your plot.

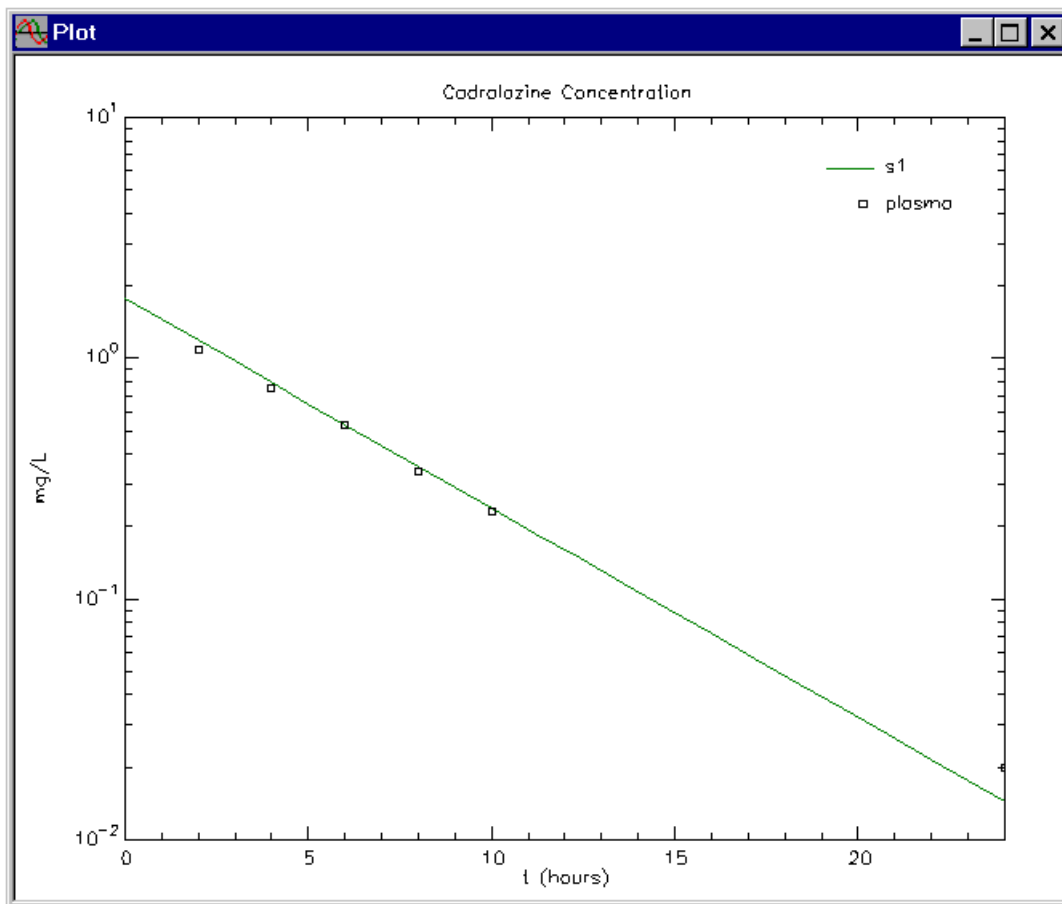
- b. In the **Plot and Table Variables** dialog box, clear the **List All Variables** check box to list only those variables associated with data.
 - c. While depressing the **Control** key on your computer click **s1** and **plasma**. Both variables will move to the **Current Selection** pane.
 - d. Click **Done**. A plot similar to your Quick Plot will appear. If it is not in semi-log mode, in the **View** menu, click **Semilog**.
4. Change the labels on your plot.
 - a. In the **Set** menu, click **Plot Labels**. The **Plot Labels** dialog box will open.
 - b. Type “Cadralazine Concentration” as the title of the plot in the **Title** box.
 - c. Type “mg/L” as the label for the Y-axis label in the **Y Axis** box. (The concentration data are in units of mg/L). The **Plot Labels** dialog box will appear as follows:




The Plot Labels dialog box is shown with the following fields and controls:

- Title: Cadralazine Concentration
- X Axis: t (hours)
- Y Axis: mg/L
- Font Size: 7
- Buttons: Done, Cancel, Help

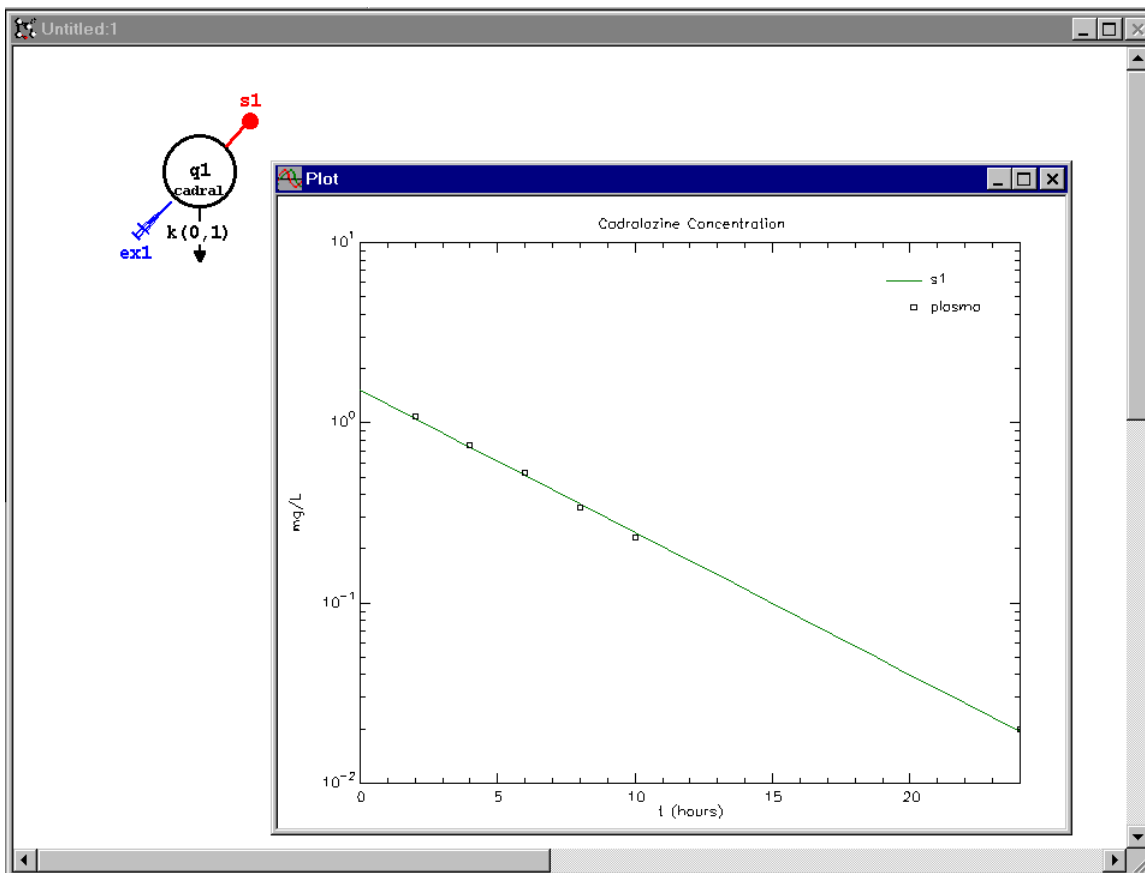
d. Click **Done**. The plot will appear as shown below:




5. With the **Plot** window open, fit the model to the data, view the solution, and record the results.
 - a. In the **Compute** menu, click **Fit**, or alternatively, on the **SAAM II Toolbar**, click **Fit** .

During a “Fit,” a **Fit Status** message will appear (on a fast computer, you may just see a flash). This is the counterpart to the **Solution Status** message you saw when you solved your model originally. The **Fitting Status** bar gives you information both on the integration part of the “Fitting,” and on the iterations. You can abort the “Fit” by clicking **Abort**.

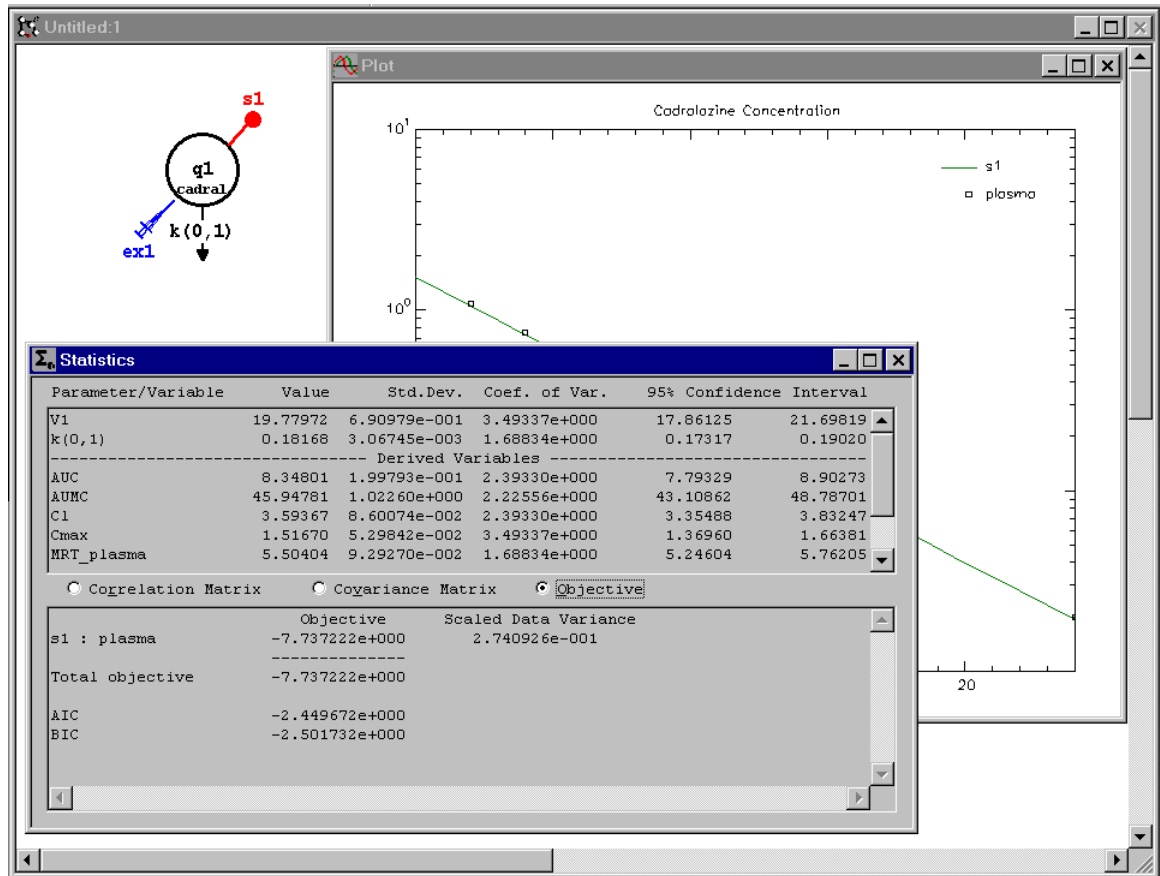
When you have fitted your model to your data, your **Drawing Canvas** with the **Plot** window should appear (after moving the **Plot** window) as follows:



It is interesting that there are no data between 10 and 24 hours. This is typical of many pharmacokinetic studies because the staff leaves in the evening. Thus the 10-hour sample is taken just before they leave, and the 24-hour sample taken when they arrive in the morning.

- b. In the **Show** menu, click **Statistics**, or alternatively, on the **SAAM II** **Toolbar**, click **Statistics** .


You can view the statistics separately, or have them appear on the **Drawing Canvas** along with the rest of the information (this may require moving some of the open windows.) An example of the latter is shown below:



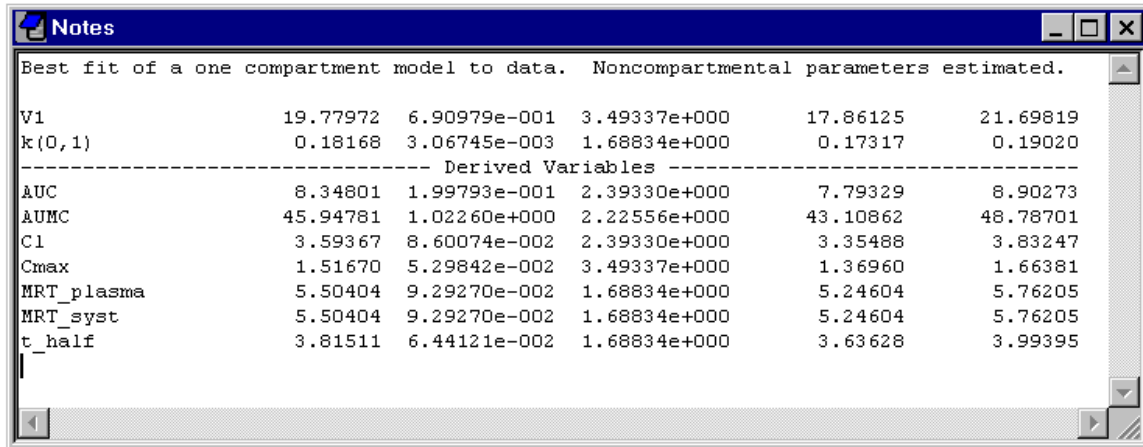
Statistics window. The **Statistics** window contains information about the “Fit.” Notice that information about the estimated value for cadralazine clearance and the other noncompartmental parameters in this patient are available under “Derived Variables” in the **Parameter/Variable** pane.



Part 6. Save the results of the Fit to Notes.

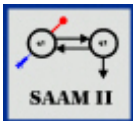
1. In the **Statistics** window, in the **Parameter/Variable** pane, select the parameters and derived variables.
2. In the **Edit** menu, click **Copy**.
3. In the **Show** menu, click **Notes**, or alternatively, on the **SAAM II Toolbar**, click **Notes** . The **Notes** window will open.
4. In the **Notes** window, type “Best fit of a one-compartment model to data. Noncompartmental parameters estimated.”

5. In the **Edit** menu, click **Paste**. The statistical information will be pasted into the **Notes** window, which will appear as follows:



Best fit of a one compartment model to data. Noncompartmental parameters estimated.

V1	19.77972	6.90979e-001	3.49337e+000	17.86125	21.69819
k(0,1)	0.18168	3.06745e-003	1.68834e+000	0.17317	0.19020
----- Derived Variables -----					
AUC	8.34801	1.99793e-001	2.39330e+000	7.79329	8.90273
AUMC	45.94781	1.02260e+000	2.22556e+000	43.10862	48.78701
Cl	3.59367	8.60074e-002	2.39330e+000	3.35488	3.83247
Cmax	1.51670	5.29842e-002	3.49337e+000	1.36960	1.66381
MRT_plasma	5.50404	9.29270e-002	1.68834e+000	5.24604	5.76205
MRT_syst	5.50404	9.29270e-002	1.68834e+000	5.24604	5.76205
t_half	3.81511	6.44121e-002	1.68834e+000	3.63628	3.99395



Notes. The **Notes** window allows you to keep track of what you did during your modeling exercise. If you save the study file, the notes are saved as part of the file so you can return to them when you run the study file at a later time.



6. Close the **Notes**, **Statistics** and **Plot** windows.

You may save your study file if you wish for future use. This can serve as a template for any analysis you may wish to do involving a one-compartment model with a bolus injection of drug.

Quit the **SAAM II Compartmental** application.

Modeling Notes:

What is the relationship between CL , $k(0,1)$ and $V1$? Remember that the differential equation for the one-compartment model is

$$\frac{dq1}{dt} = -k(0,1)q1 + \text{Dose}$$

The solution to this equation is a single exponential function

$$q1 = \text{Dose} \cdot \exp(-k(0,1) * t)$$

and the measurement sample $s1$ is thus

$$s1 = \frac{q1}{V1} = \frac{\text{Dose}}{V1} \exp(-k(0,1) * t)$$

An alternative parameterization of this model is

$$s1 = \frac{q1}{V1} = \frac{\text{Dose}}{V1} \exp\left(-\frac{Cl}{V1} * t\right)$$

because $Cl = k(0,1) * V1$. That is, both the parameter pairs $(k(0,1), V1)$ or $(Cl, V1)$ alternatively define completely the one-compartment model. If you choose to use the second parameterization, you will have to open the **Loss Attributes** dialog box associated with $k(0,1)$, and type the equation " $k(0,1)=Cl/V1$ ". In the **Parameters** dialog box, $k(0,1)$ will no longer appear on the parameter list since it has been defined by an equation. The parameter that will appear is clearance, Cl .

Essential Points to Remember

- Derived variables (noncompartmental parameters) can be defined in your model.
- The **Notes** window provides a convenient way to keep track of your modeling exercise.
- Your model can be re-parameterized in terms of volume and clearance.
- This model can serve as a template for any drug study where the drug was administered as a bolus, and the decay was monoexponential.

**Appendix: Obtaining Initial Parameter Estimates
for the One-Compartment Model (One-Exponential Model)**

The key to understanding how initial parameter estimates can be obtained for the one-compartment (or one-exponential) model lies in understanding the notion of half-life (sometimes called the half-time). The half-life is defined as the time it takes for one-half of the material remaining in a system to irreversibly leave the system. The reason why this works so well in the one-compartment case is that the data, when plotted semi-logarithmically, appear as a straight line. Thus, as will be seen, one can pick an arbitrary point on this line, and one half of this material represented by this point will appear on the line as a time equal to the “half-life” later.

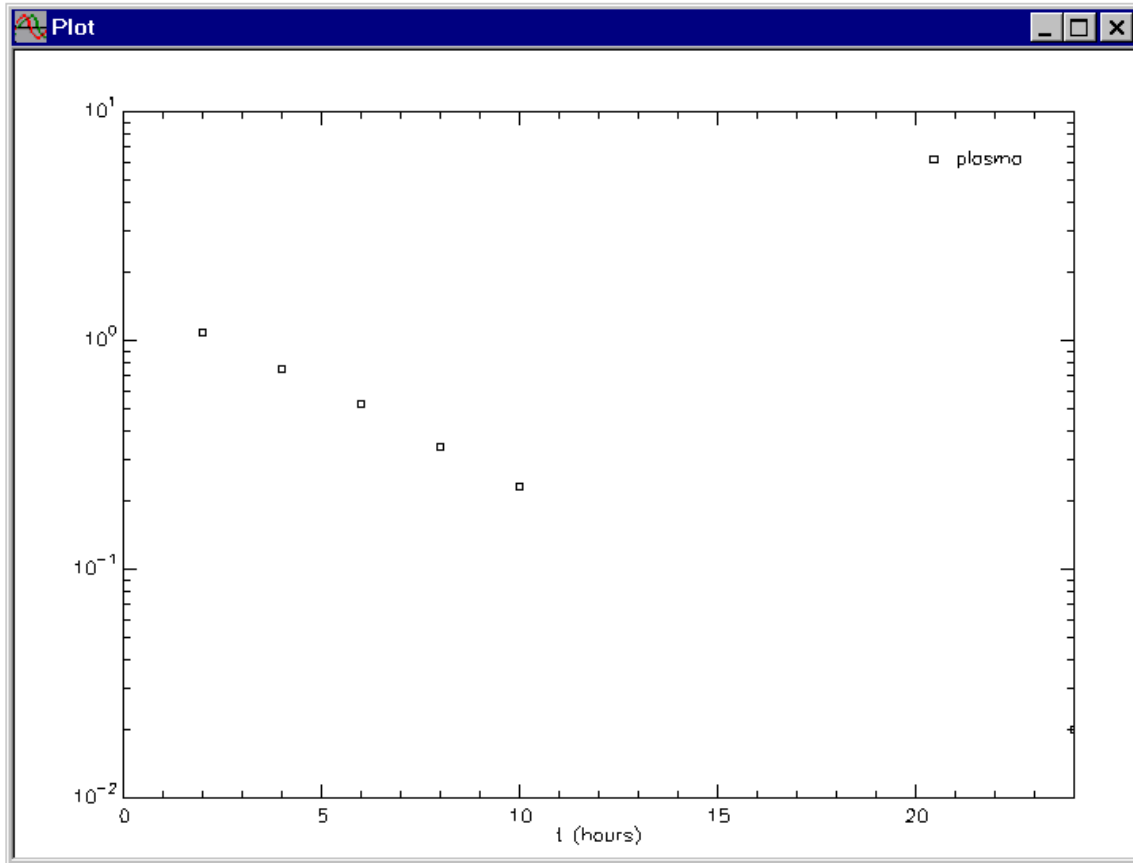
In this appendix, you will learn how to obtain the initial estimates in the following two situations:

- bolus injection of drug into plasma, and serial plasma samples taken; and
- constant infusion of drug into plasma, and serial plasma samples taken.

The bolus injection will be discussed first since, when plotted semilogarithmically, the data appear as a straight line. This is not the case with the constant infusion.

Bolus injection into plasma

If you plot the cadralazine data in semi-log form, you will obtain the following:



The data appear to lie on a straight line. Why?

The answer comes from the fact that for the one-compartment (monoexponential) model, the semi-logarithmic transformation results in a linear plot. This can be explained as follows:

Suppose you write the monoexponential decay

$$y(t) = Ae^{-\alpha t} \quad (1)$$

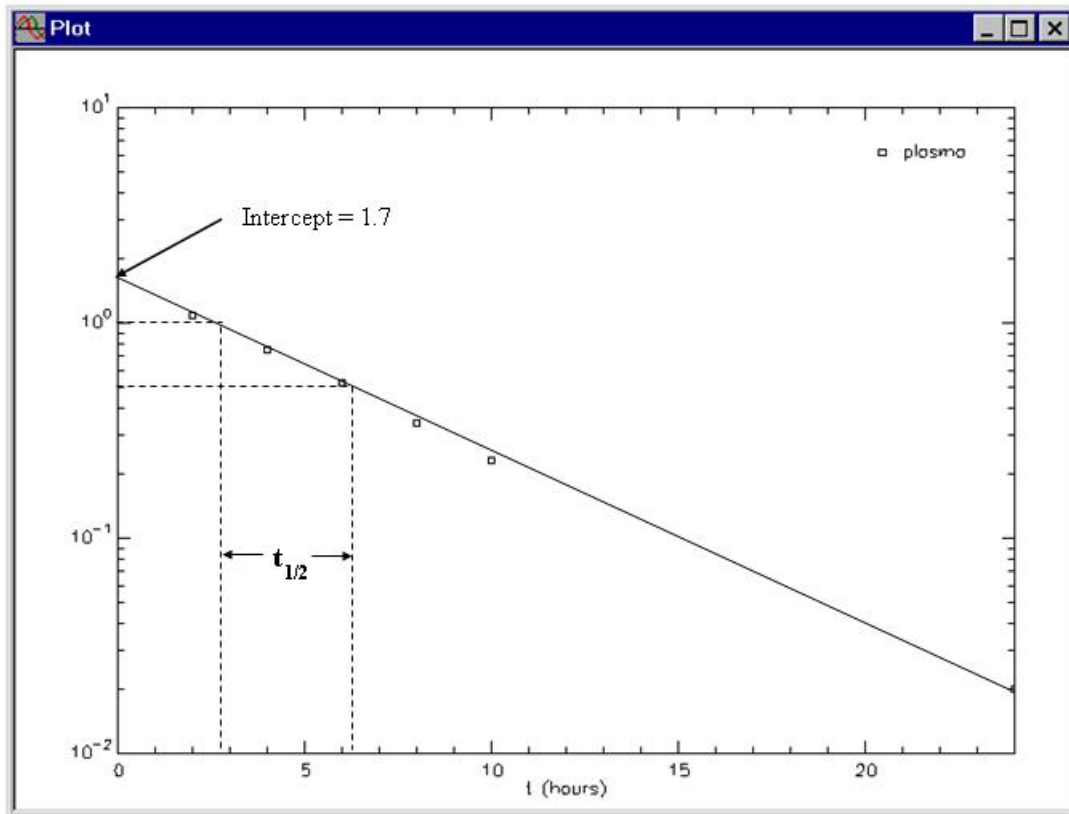
Taking the log of both sides of (1), you will have

$$\ln(y(t)) = \ln(A) - \alpha \cdot t \quad (2)$$

This is a straight line whose slope is $-\alpha$ and whose intercept with the y-axis is $\ln(A)$.

How can one find α and A ?

The first thing you do is to draw a straight line through the data (as shown in the figure below). Where the line intersects the y axis will provide an estimate for A . This is shown graphically in the following figure.



To find an estimate for α , pick an arbitrary point on the line shown above; say this occurs at time t^* (in the above, the arbitrary point's y-axis value is 1 and t^* is about 2.8 hours). Then the value of $y(t)$ defined in (1) is

$$y(t^*) = Ae^{-\alpha t^*} \quad (3)$$

One-half of this material (which in the above would be 0.5) is

$$\frac{y(t^*)}{2} = \frac{A}{2} e^{-\alpha t^*} \quad (4)$$

Write $t_{1/2}$ for the time of the half-life, i.e. the time it takes for one half of the material in the system to irreversibly leave the system. Then from (3), the amount of material in the system is given by

$$y(t^* + t_{1/2}) = Ae^{-\alpha(t^* + t_{1/2})} \quad (5)$$

Equating (4) and (5)

$$\frac{A}{2} e^{-\alpha \cdot t^*} = A e^{-\alpha \cdot (t^* + t_{1/2})} \quad (6)$$

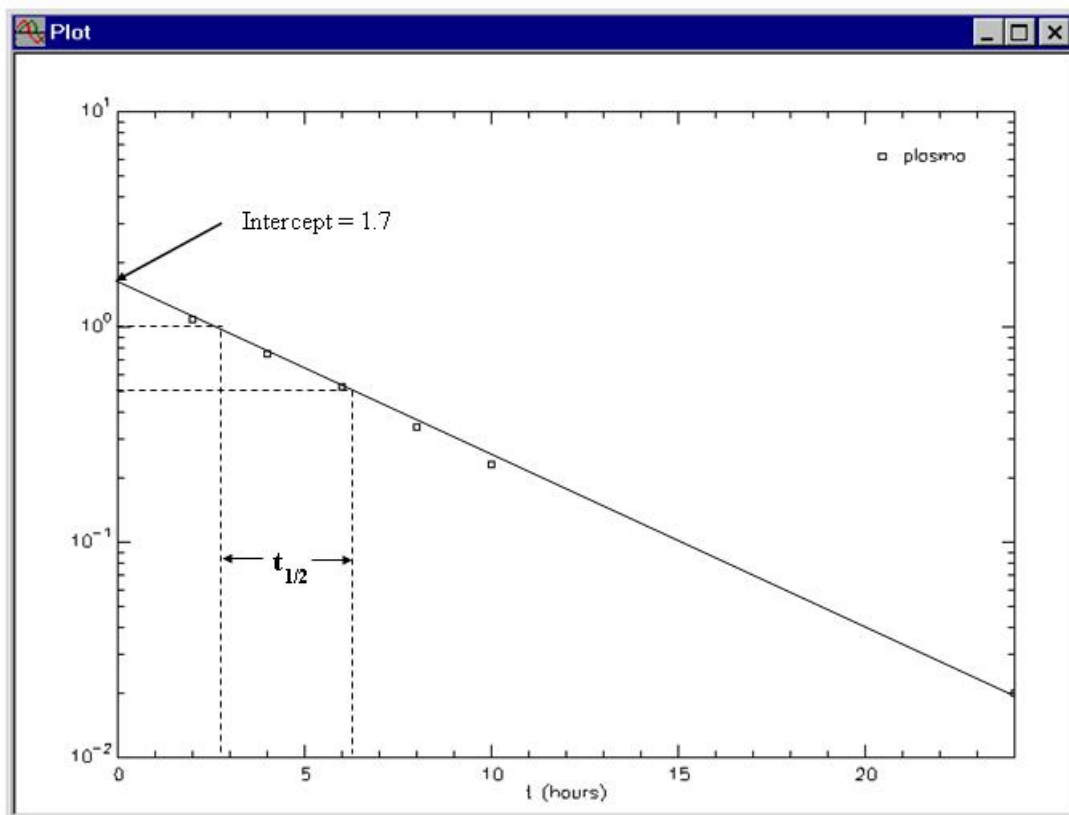
Rewriting (6)

$$\frac{1}{2} = e^{-\alpha \cdot t_{1/2}} \quad (7)$$

It is important to notice that both A and $e^{-\alpha \cdot t^*}$ no longer appear in the equation. The only terms remaining are α and $t_{1/2}$. Equation (7) can be rewritten to express the relationship between α and $t_{1/2}$

$$\alpha = \frac{\ln(2)}{t_{1/2}} \approx \frac{0.693}{t_{1/2}} \quad (8)$$

These steps are illustrated in the previous figure reproduced below for convenience:



In this figure, the intercept with the y-axis is 1.7. To estimate the half-life, you can start with 1.0 (written 10^0 in the figure) as indicated. This occurs at about 2.8 hours as

indicated by the dashed line intersecting the x-axis at 2.8 hours. Half of 1.0 is 0.5; this occurs at about 6.2 hours again as indicated by the dashed line intersecting the x-axis at 6.2 hours. Thus the half-life is 6.2 - 2.8 or 3.4 hours. An estimate for α can be obtained from $\ln(2)/3.4$ which is about 0.20.

If you are fitting the monoexponential (3) to the data, then 1.7 and 0.2 would provide initial estimates for A and α , and you can proceed to fit the model to the data. What happens in the case of the one-compartment model is the following:

Your one-compartment model represents the differential equation

$$\frac{dq_1}{dt} = -k(0,1) \cdot q_1 \quad q_1(0) = D \quad (9)$$

where, in this equation, D is the dose of the drug given as a bolus. The solution to this equation is

$$q_1(t) = D \cdot e^{-k(0,1)t} \quad (10)$$

However, the data are concentration, not mass, and the measurement equation is thus

$$s_1 = \frac{D}{V_1} \cdot e^{-k(0,1)t} \quad (11)$$

Compare (1) and (11). The equations $y(t)$ and s_1 describe the same set of data; one is the exponential model and the other the solution of the differential equation. Since the exponentials must be the same, one has immediately that an estimate for $k(0,1)$ is α . Also, A equals D/V_1 . Thus an estimate for the volume of the compartment V_1 , is D/A . It is absolutely essential to know that, to estimate the volume of the compartment, you must know the dose. If you do not know the dose, you cannot estimate the volume.

For this example, an estimate for $k(0,1)$ is 0.2. The dose was 30mg, and the units of the data are mg/L. An estimate for A is 1.7, so the estimate for V_1 is D/A , 30/1.7, which is about 17L.

Summarizing, the steps in obtaining the initial estimates for the one-compartment model are as follows:

- Plot the data on semi-log paper to see whether or not they lie on a straight line.
- Draw a straight line through the data; extend the line to intersect with the y-axis.
- Calculate the half-life $t_{1/2}$ as described above.
- Note where the line intersects the y-axis.
- Estimate the volume and $k(0,1)$ (or A and α) as described above.

Constant infusion into plasma

The case when the drug is administered as a constant infusion into plasma represented by a one-compartment model is not as straightforward as the bolus injection. The reason is that the semi-logarithmic transformation does not result in a linear plot. This is easily seen when you realize that the equation for a single exponential rise is

$$y(t) = A \cdot (1 - e^{-\alpha t}) \quad (12)$$

If, as in (3), you take the logarithm of both sides of (12), the right hand side does not collapse into the equation for a straight line!

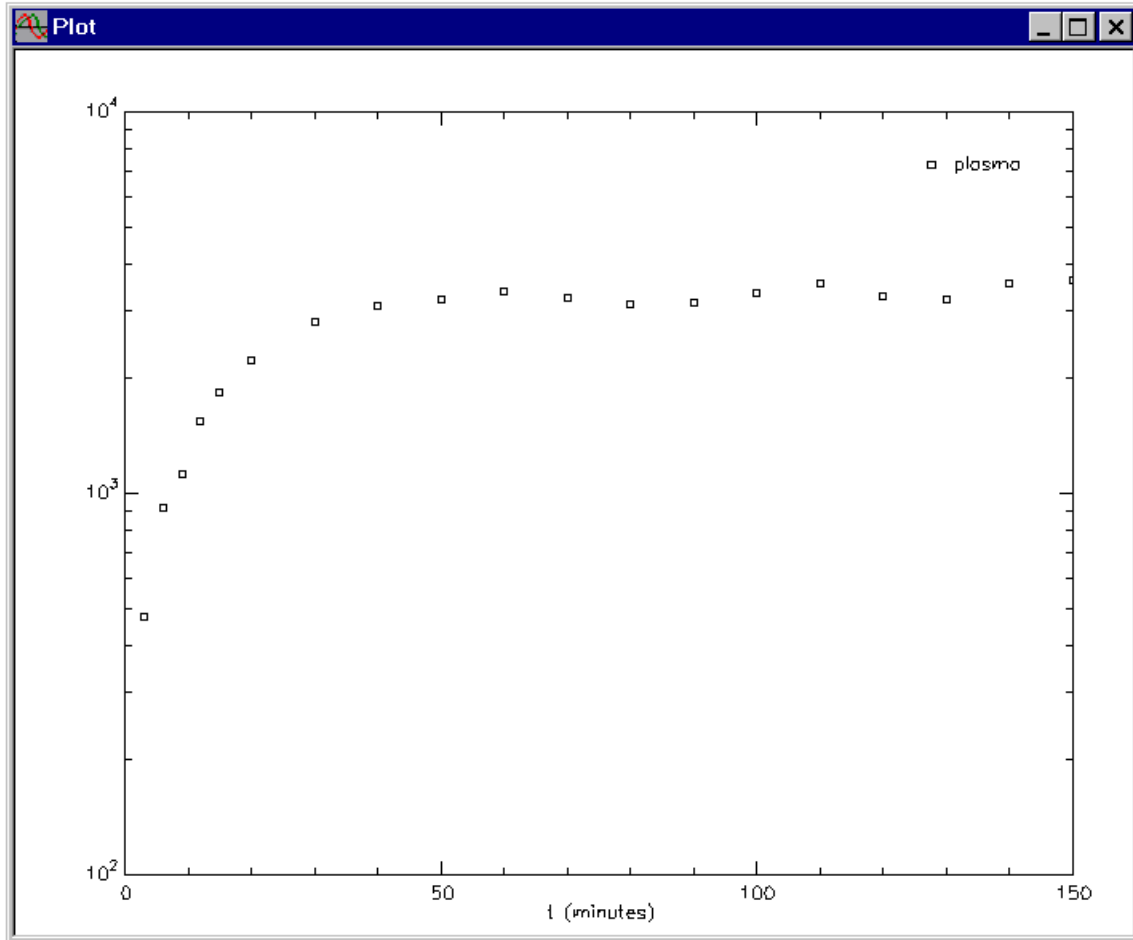
If you examine (12) more closely, you will see that $y(0)$ equals 0 which, in the case of the constant infusion, it should. In addition, A is the plateau value since for large values of t , the exponential term is close to zero. Thus for the rising data, an estimate for A can be obtained by estimating the plateau value of your data.

The other important observation to make is that if you subtract A from (12), you will have

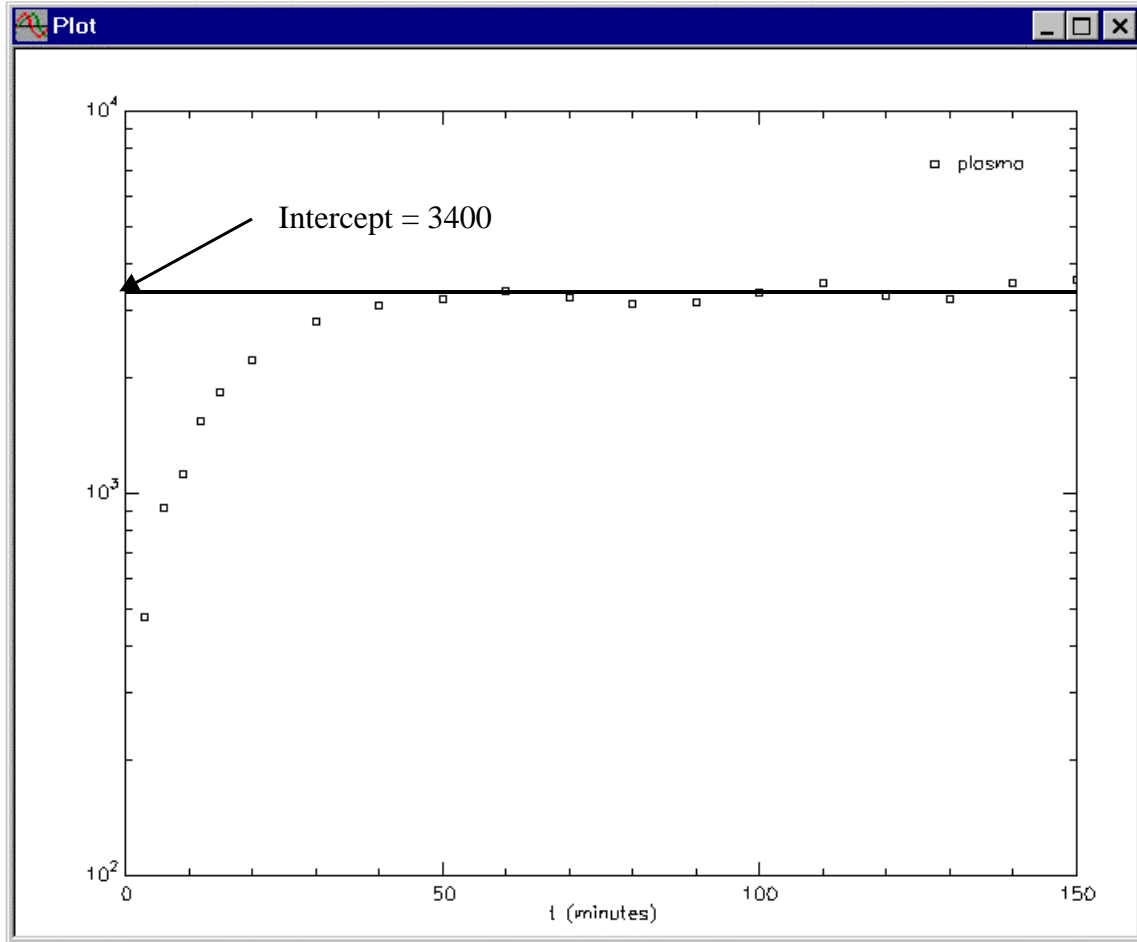
$$y^*(t) = -A \cdot e^{-\alpha t} \quad (13)$$

which is a monoexponential the negative of which is monoexponentially decaying. Thus the hint on how to obtain the initial estimate for α for the monoexponentially rising data is the following: if you transform your data by first subtracting A from them, and then multiplying by -1 , the initial data will decay exponentially, and you can use the above to estimate α .

Consider the following example of a set of data. These data were obtained following an infusion of 500,000 units/min into plasma. You cannot really tell from looking at them whether they rise monoexponentially or biexponentially. However, you should always start with the one exponential (one-compartment) model.



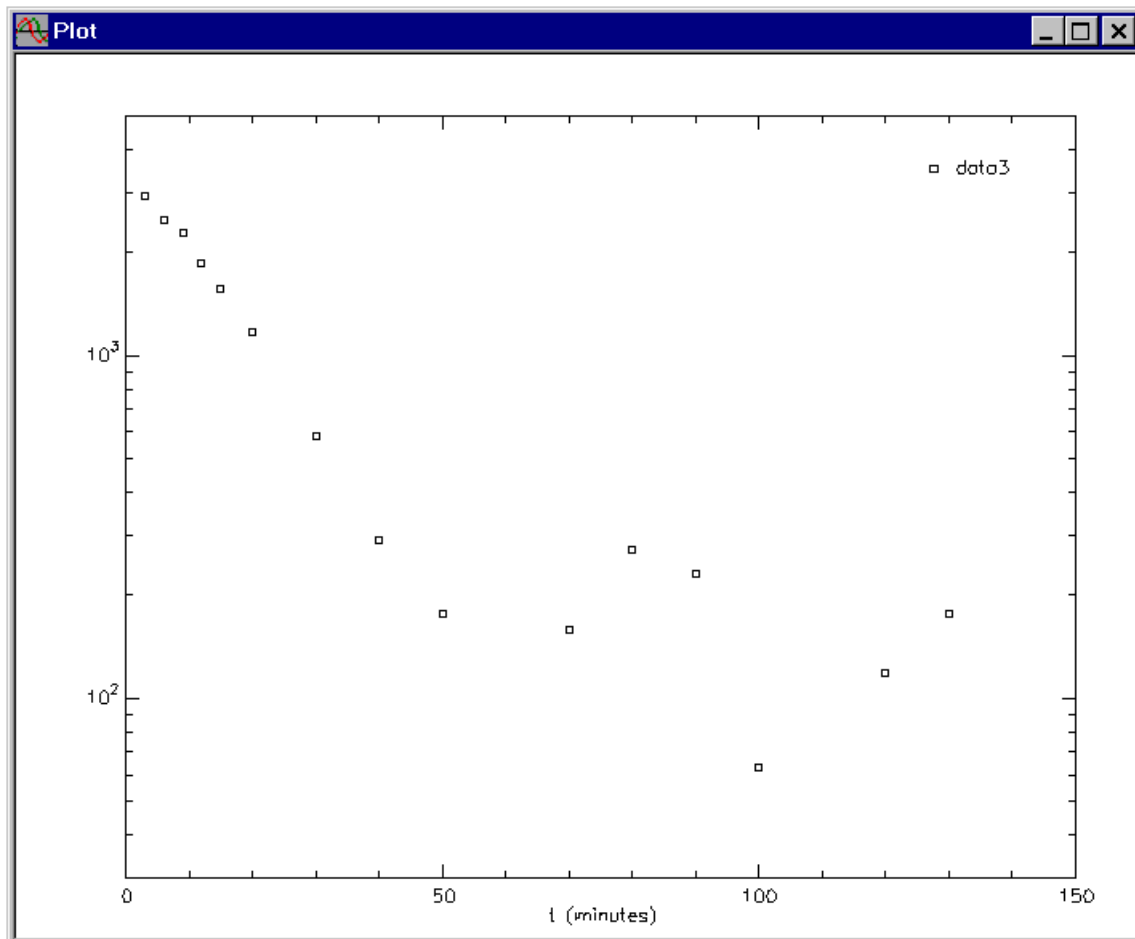
These data are plotted semi-logarithmically, and it is clear, unlike the first case, they do not lie on a straight line. However, as shown below, an estimate for the plateau value of 3400 can easily be obtained:



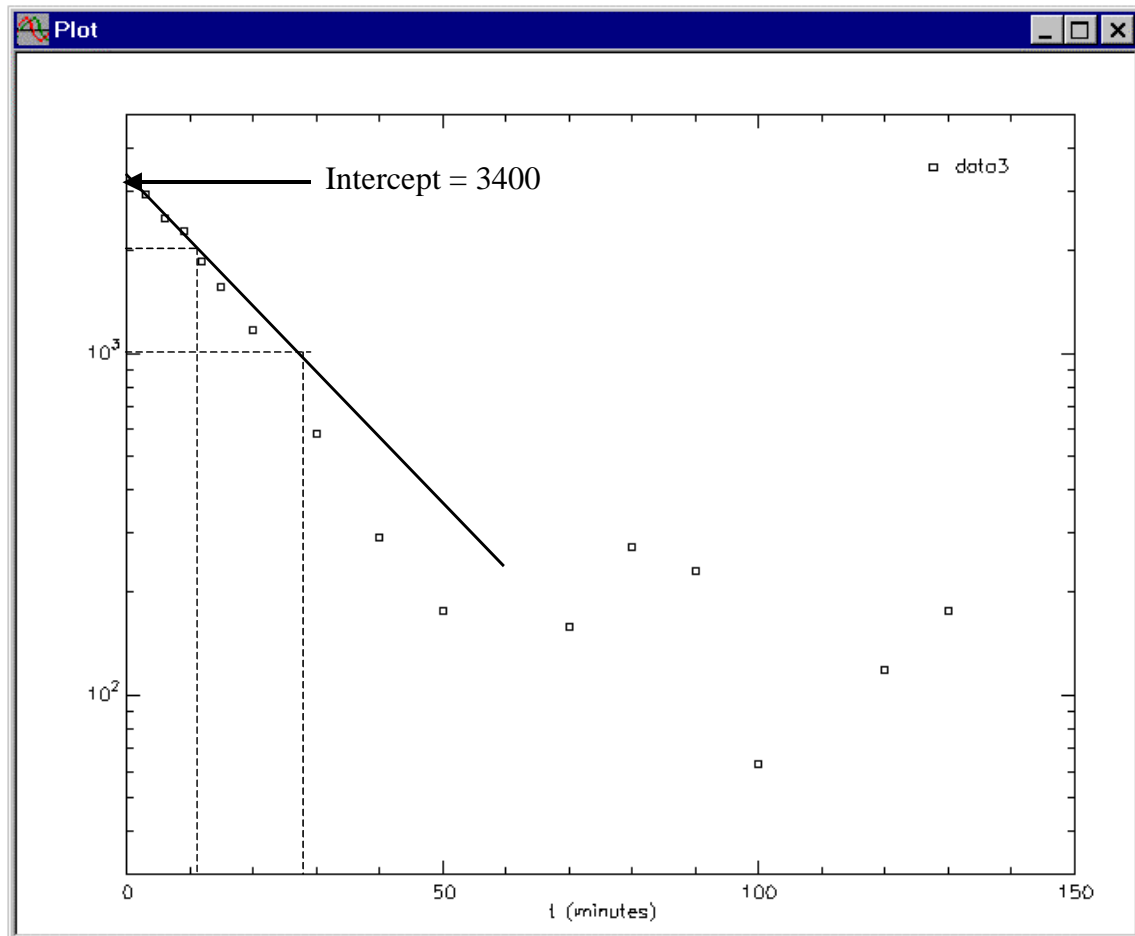
The plateau value can be subtracted from the actual data and multiplied by -1; this is shown in the following:

t	plasma	data-3400	-(DATA-3400)
3	473	-2927.00	2927.00
6	915	-2485.00	2485.00
9	1127	-2273.00	2273.00
12	1549	-1851.00	1851.00
15	1840	-1560.00	1560.00
20	2229	-1171.00	1171.00
30	2817	-583.00	583.00
40	3111	-289.00	289.00
50	3223	-177.00	177.00
60	3399	-1.00	1.00
70	3241	-159.00	159.00
80	3128	-272.00	272.00
90	3169	-231.00	231.00
100	3337	-63.00	63.00
110	3546	146.00	-146.00
120	3281	-119.00	119.00
130	3223	-177.00	177.00
140	3543	143.00	-143.00
150	3624	224.00	-224.00

If you plot $-(DATA-3400)$, you will obtain the following:



Two important observations need to be made. First, the “noise” in the data after 50 minutes is due to the fact the data are on the plateau. Second, as the plateau is reached there appears to be curvature in the “decay.” Thus the best estimates for the initial decay will come from the earlier time points. When drawing the line through the data, these points should have more influence. This is shown below:



There are some additional things to notice in the above plot. First, the straight line intersects the y-axis at about 3400; this is as would be predicted. Second, the line through the initial “data” had to be extended in order to obtain the half-life estimate. The half-life is calculated by starting from 2000 (the y-axis value), which occurs at 6 minutes, and ending at 1000 (the y-axis value), which occurs at 18 minutes. The half-life is thus 12 minutes, and an estimate for α can be obtained from $\ln(2)/12$ which is about 0.06.

Thus if you are working with the monoexponential rise model, equation (12), your initial estimates for A and α would be 3400 and 0.06 respectively. What about the one-compartment model? You need estimates for the volume, Vl , and the rate constant $k(0,1)$. As with the previous case, an estimate for $k(0,1)$ is α . The problem, then, is to estimate the volume.

To estimate the volume requires some knowledge of estimating the noncompartmental parameters. It is known that the clearance rate, Cl , can be estimated as the quotient of the infusion rate and plateau value. In this case, the infusion rate is 500,000 units/min and the plateau is 3400. Thus

$$Cl = \frac{\text{Infusion rate}}{\text{Plateau}} = \frac{500000}{3400} = 147 \quad (14)$$

But the clearance rate is also the product of the volume and $k(0,1)$. That is, if VI is the volume of the compartment,

$$Cl = k(0,1) \cdot VI \quad (15)$$

Knowing that the estimate for $k(0,1)$ is 0.06 and the estimate for Cl is 147, an estimate for VI of 2450 can be obtained.

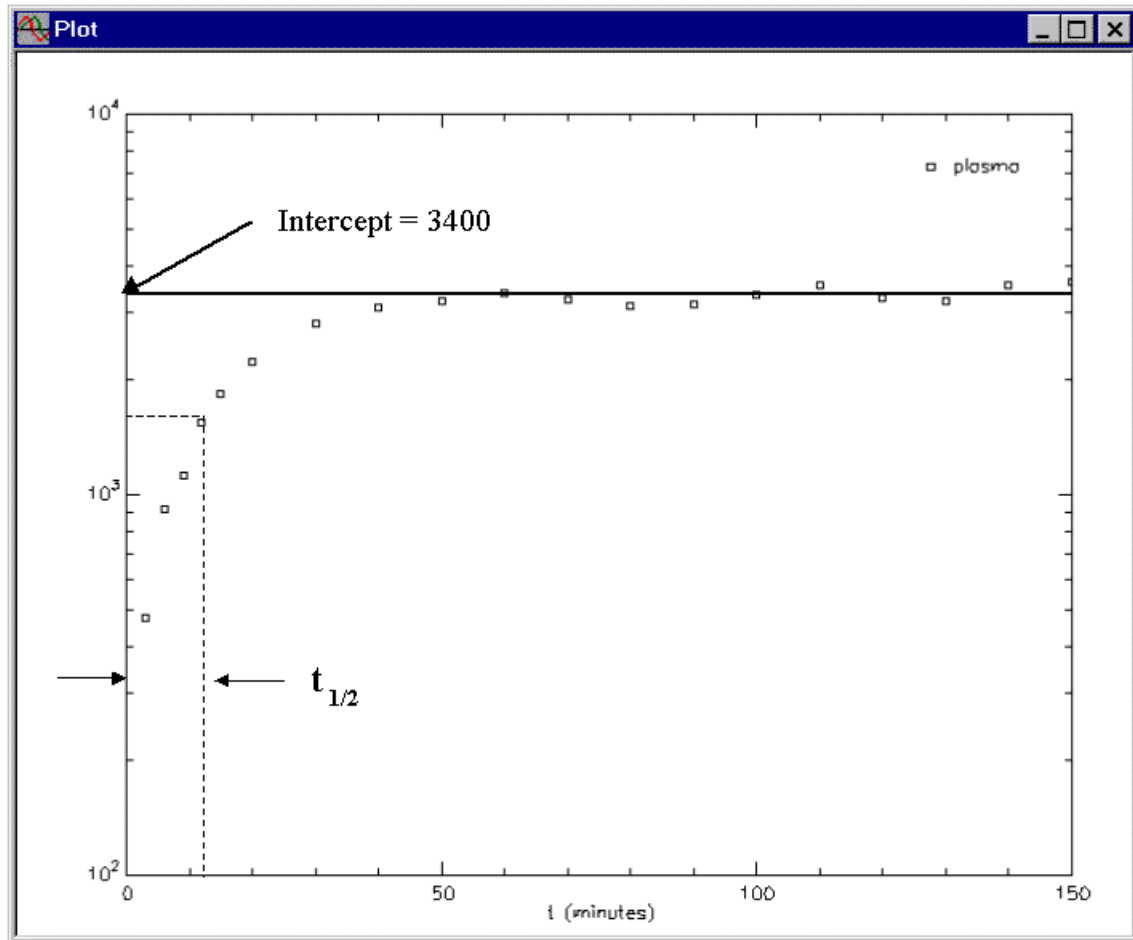
Summarizing: The steps in obtaining the initial estimates for the one-compartment model following a constant infusion are as follows:

- Plot the data on semi-log paper.
- Estimate the plateau value (which is A in the monoexponential model)
- Subtract the plateau value from each datum, and multiply the result by -1.
- Plot the modified data on semi-log paper.
- Draw a straight line through the initial decaying data (it should intersect at approximately your estimate of the plateau value.
- Calculate the half-life along the line, and estimate $k(0,1)$ (or α) as described above.
- Estimate the volume as described above by first estimating the clearance rate, and then the volume.

Question: is there a quicker way to estimate α or $k(0,1)$? That is, do I always have to calculate the “modified” data? The answer is yes, there is a quicker way, but the estimate is not as robust as the above, and may require some hand-fitting before proceeding.

The idea is the following. You can estimate the time it takes for the data to rise half way to the plateau. In this case, the plateau value is 3400, so half way is 1700. As indicated on the following figure, the time, the half-life, to go from zero to 1700 is approximately 13 minutes. Using the relationship between the half-life and α , one can estimate α , or $k(0,1)$, as $\ln(2)/13$ which is approximately 0.053. This is close to the estimate obtained above, and is clearly sufficient as a starting point.

The situation is shown in the following figure:



Thus it is safer to use the first method in the case of the constant infusion. However, this method is much quicker and while it may require some hand-fitting to adjust the estimates, it is usually close enough that you can proceed with fitting your model to your data.

Data for this case study

This data file also contains the equations for the noncompartmental parameters.

DATA

#Data used for Cadralazine Case Study

#Cadralazine1 from Wakefield et al., Applied Statistics, 43(1): 201-221, 1994.

The dose for this study was 30 mg

(FSD 0.1)

t plasma

0 n

2 1.09

4 0.75

6 0.53

8 0.34

10 0.23

24 0.02

END

CONST Dose 30

#

Equations for the noncompartmental parameters

#

$Cl = k(0,1) \cdot V1$

$C_{max} = Dose / V1$

$t_{half} = \log(2) / k(0,1)$

$AUC = Dose / (V1 \cdot k(0,1))$

$AUMC = Dose / (V1 \cdot k(0,1) \cdot k(0,1))$

$MRT_{syst} = AUMC / AUC$

$MRT_{plasma} = 1 / k(0,1)$

This page is intentionally left blank