Mathematical Journeys I

Lab 9

Hemodiaylsis

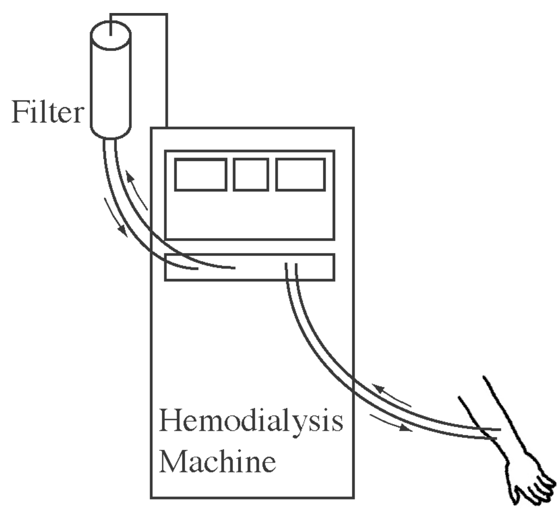
Introduction

The kidneys provide the essential function of removing toxins from the body. The incidence of renal (kidney) failure is increasing, in part due to the increasing number of older people. Medical costs impact federal, state and private funding sources as well as personal finances.

At this point in time, renal transplant and dialysis are the only medical alternatives. The number of kidneys needed is greater than the number of available healthy organs. Thus, dialysis is frequently used to counteract the effects of renal failure. There are two types of dialysis – hemodialysis and peritoneal dialysis. Hemodialysis will be the focus of this laboratory.

In hemodialysis, the patient is connected to a hemodialysis machine. The patient's blood is directed to flow through the machine, which filters away toxins. The blood is then transferred back to the body with the toxins removed. Patients usually receive dialysis treatments three times a week. Each treatment can last 3 to 4 hours.

Figure 1



A dangerous side effect of dialysis is that blood clots can form. This not only poses a direct risk to the patient, but also impedes the flow of blood through the dialysis machine. Anticoagulants such as heparin are used to prevent blood clots. Medical staff must monitor the dialysis treatment, balancing the danger from clot formation with the danger from premature termination of the treatment.

Technology Problem

As a medical expert, you have been called in as a consultant regarding dialysis treatment for a kidney patient. You will need to determine the appropriate heparin loading dose and constant heparin infusion rate for a 4.5-hour dialysis treatment. Unfortunately, the process to identify the appropriate doses is very experimental. Your job will be to develop a model to calculate the correct initial and continuing doses of heparin. This is important for the health of the patient because heparin modeling has made it possible to reduce the amount of heparin required for the dialysis treatment and yet achieve the desired effect.

To solve this problem, you will apply the scientific method. The scientific method has five steps – problem, question, hypothesis, test, and decision. The first two steps of the scientific method (problem, question) depend on exploring the situation and developing a better understanding of the problem. You may want to meet with your professor and develop a timeline with specific objectives and deadlines. You will probably begin exploring the problem with some bibliotechnology research.

Bibliotechnology Research

To begin to understand this problem, you will first need to establish a baseline of general knowledge about hemodialysis. Some questions you may want to explore include the following.

What is end-stage renal disease (ESRD)?
What is the demographic profile of an ESRD patient?
What is the treatment for ESRD?
What is the cost of ESRD treatment?
What is the mortality rate for an ESRD patient?

After you gain a general idea of renal disease, you can research more specific information about hemodialysis.

What is the procedure for hemodialysis?
What are the risk factors for hemodialysis?
Can blood clots form during hemodialysis?
How are blood clots prevented during hemodialysis?
What is an anticoagulant?
What is heparin?
What are the risk factors for heparin?
How is heparin administered to the patient?
What is pharmacokinetics?

As you continue your research, you may encounter unfamiliar vocabulary. It will be helpful to begin assembling a glossary of pertinent words and expressions with their definitions.

Clearance
WBPTT: Whole Blood activated Partial Thromboplastin Time
Pharmacokinetics
International Unit
Sensitivity
Elimination Rate Constant
Half-Life
End-stage renal disease (ESRD)
Dialysis
Hemodialysis
Anticoagulant
Heparin
Nephron

You may find the following web sites helpful for your research. This list is not meant to be complete. You are encouraged to search the web for other relevant sites.

- http://www.floridahealthsite.org/dialysis/dial_nih.html
- http://www.thekidney.com/dialysis.htm
- http://www.niddk.nih.gov/health/kidney/pubs/yourkids/index.htm
- http://nephron.com/
- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

Mathematics Tools

In the investigation of this problem, you will need to select mathematics tools that best fit the problem, that help explain the problem, and that provide a solution to the problem. You may wish to review functions, exponential functions, integration by substitution, differential equations, and statistics.

Model Portfolio

As part of the solution to the technology problem, you will need to create a model portfolio. The model portfolio should contain a thorough description of the technology problem and its identifying characteristics. You need to explain the mathematics, technology, and science you use to solve the problem. In addition, you need to include the mathematical and/or physical models you create. It is important that you keep a careful record of your work. It should be complete enough so that someone else could follow your work step by step. The model portfolio will be very helpful when you present your thesis defense. Remember that you are a medical consultant and may need to explain your recommendations to other medical personnel, to the patient, or to the patient's family and support system.

Model Development

The third step of the scientific method is to develop a hypothesis about the technology problem. You can think of the model(s) you create as a hypothesis. Your model constitutes a proposal that describes and explains the technology problem.

In order to develop your model, you will need to explore two aspects of dialysis – the amount of time it takes for blood clots to form and the elimination rate constant for a given rate of heparin infusion.

Section I
Coagulation time

You will need to determine a measure of the clotting rate of blood for your patient. Two different measures in use are the activated partial thromboplastin time (aPTT) and the whole blood activated partial thromboplastin time (WBPTT). In this laboratory, you will use the WBPTT approach.

To determine a patient's WBPTT, test tubes are inserted into a heating block maintained at $37^\circ C$. Each tube contains 0.2 mL of a particular clotting reagent such as heparin. A tube is selected, and 0.4 mL of whole blood drawn from the patient is added to the tube containing the reagent. The reagent and whole blood are mixed and then returned to the heating block to be timed with a stopwatch. The tube is then checked every 5 seconds until a clot forms, at which time the stopwatch is stopped. The time taken for the clot to form is defined to be the WBPTT.

Heparin affects the clotting mechanism very soon after it is administered. When given intravenously, it is well distributed in the circulating blood within three minutes. The coagulation time depends on several variables. To determine an equation for coagulation time, begin with the following variables.

BL = Baseline WBPTT, i.e. the coagulation time without heparin.

D = Dose of heparin administered, measured in international units (IU).

R = Response, measured in seconds. Response is defined to be the difference in WBPTT with and without heparin. Thus, response R is described by

$$R = \text{WBPTT}(\text{with heparin}) - BL \qquad (1)$$

S = Sensitivity, measured in seconds per IU. This value indicates how quickly heparin is absorbed by an individual patient.

The response R can be mathematically related to the dose D and sensitivity S with a simple linear model. The results of experimental research indicate that a scatter plot of data consisting of various doses of heparin and corresponding response times exhibits a strong linear relationship between response time and dose. In statistical terms, it can be said that the correlation coefficient is very close to the number 1. Thus, the theoretical model for the relationship between response and dose is described by

$$R = S \cdot D \qquad (2)$$

Note that the sensitivity of the individual patient serves as the slope of the straight-line relationship between dose and response.

In practice, the sensitivity for an individual patient can be determined as follows.

- Measure a baseline WBPTT without heparin
- Administer a dose D of heparin, e.g. D = 2000 IU
- After 3 minutes (when the heparin is uniformly distributed in the circulating blood), measure the WBPTT again.
- Substitute the values for the dose and response into Equation (2) and calculate S.

Exercise 1

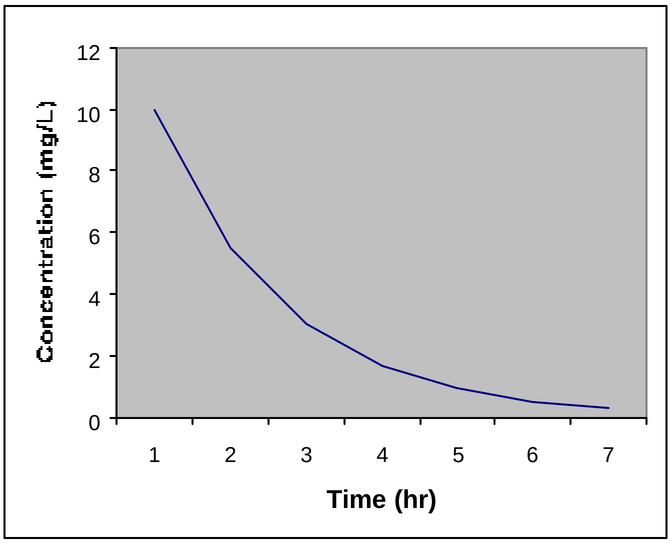
Determine the sensitivity of a patient with a baseline of 70 seconds who has a WBPTT of 160 seconds after a dose of 2000 IU of heparin.

Section II
The elimination rate constant

Part A A simple pharmacokinetic model

To better understand the elimination rate constant for dialysis, it will be helpful to first explore a simple pharmacokinetic model based on a single injection of a drug. The drug-plasma concentration measures the concentration of a drug in the blood plasma. Plasma is the liquid portion of the blood. A concentration-time plot may be constructed by administering a dose of the drug and then measuring its concentration in the blood plasma at regular intervals after the injection. For simplicity, assume that the drug enters the bloodstream instantaneously. Then the graph below describes the drug-plasma concentration over time.

Figure 2
Concentration vs. Time



The graph in Figure 2 represents a first-order reaction, since the drug-plasma concentration decreases at a rate proportional to the concentration present.

Exercise 2

Write a first-order differential equation to describe the reaction and solve your equation.

In Exercise 2, you calculated the following general solution of your differential equation

$$C_t = C_0 e^{(-kt)}$$

In this context, the equation is called a concentration equation for first order elimination of the drug. The value k in this equation is the elimination rate constant.

Exercise 3

Construct a table of values for the concentration of a drug every hour for 6 hours following administration of a dose that achieves an initial drug-plasma concentration of 15 mg/liter. Assume that the elimination rate constant is 0.6. Plot the graph of drug-plasma concentration over time.

Part B A pharmacokinetic model for heparin clearance

The simple model of drug concentration described above, for which the drug-plasma concentration decreases at a rate proportional to the concentration present, results in a model of exponential decay. By contrast, the first-order model for heparin clearance asserts that the rate of change in the amount of heparin in the blood during continuous infusion at a constant rate is the difference between the rate at which it is infused and the rate at which it is absorbed. The latter is proportional to the drug-plasma concentration, as was shown in the simple pharmacokinetic model. To model continuing infusion, you will need the following variables. Let

M = amount of circulating heparin at any time t

V = plasma volume (volume of plasma in the patient's bloodstream)

C = drug-plasma concentration (concentration of heparin in the patient's plasma)

I_R = constant infusion rate

k = clearance constant (elimination rate constant)

Thus, heparin elimination during continuous infusion at a constant rate is modeled by the first-order differential equation

$$\frac{d(M)}{dt} = I_R - kC$$

Observing that $M = C \cdot V$, it follows that

$$\frac{d(C \cdot V)}{dt} = I_R - kC \qquad (3)$$

Since M is equivalent to D in Equation (2), we see that

$$M = D = R/S$$

So that Equation (3) may be written

$$\frac{d}{dt}\left[\frac{R}{S}\right] = I_R - k\frac{R}{V \cdot S}$$

or defining a new elimination rate constant to be

$$K = \frac{k}{V} \quad \text{we obtain}$$

$$\frac{dR}{dt} = I_R \cdot S - K \cdot R \tag{4}$$

During the course of a dialysis, the plasma volume V can be assumed to be constant, so that K is constant. Equation (4) can be solved to obtain the result

$$R = R_0 e^{-Kt} + \frac{I_R S}{K}\left(1 - e^{-Kt}\right) \tag{5}$$

Exercise 4

Verify that Equation (5) is the general solution to Equation (4).

To emphasize that R is a function of t in the case of continuous infusion, replace R in Equation (5) with R_t to obtain

$$R_t = R_0 e^{-Kt} + \frac{I_R S}{K}\left(1 - e^{-Kt}\right) \tag{6}$$

Part C Constant infusion rate

The exponential relationship expressed by Equation (6) implies that R_t will gradually decline to a steady state. It is easily verified that as time increases without bound the steady state value of R_t will be

$$\frac{I_R S}{K}$$

The patient for whom you are consulting will be administered an initial dose of heparin (loading dose) followed by continuous infusion of heparin at a constant rate. The primary physician will specify a desired coagulation time, i.e. a value for the WBPTT. The desired loading dose to ensure this degree of anticoagulation can be determined from Equations (1) and (2) using the patient's measured sensitivity and the desired response R_D (R_D= Specified WBPTT – BL, R_D= SD). During continuous infusion, the response time will be maintained at a constant value, $R_t = R_D = R_0$.

Exercise 5

Substitute $R_t = R_D = R_0$ in Equation (6) and solve for I_R, the constant infusion rate.

Your answer to Exercise (5) provides the formula to determine the constant infusion rate. Note that for precise anticoagulation, it is necessary to know only the patient's sensitivity S and the elimination rate constant K.

Part D Initial estimate of K

An initial estimate of the elimination rate constant K can be determined by measuring the WBPTT at regular intervals during a dialysis treatment. At each stage, set t = 1 (i.e. recalculate K at the beginning of each hour during the dialysis). At the end of the dialysis treatment, calculate the mean of the experimental values of K and use that value as the elimination rate constant for the next treatment. To determine formulas for the elimination rate constant K, you will need to consider two aspects of the dialysis treatment – the period of time when heparin is continuously infused and the following period of time when the infusion has been discontinued.

1) Continuous infusion at a constant rate

To calculate the elimination rate constant K while heparin is being infused, rewrite Equation (6) in the following form:

$$K = \left[\frac{I_R S}{R_0}\right]\left[\frac{1 - e^{-Kt}}{\frac{R_t}{R_0} - e^{-Kt}}\right]$$

Assuming an incremental model in which R_0 always refers to the response from the previous time period, i.e. $R_0 = R_{t-1}$, you can obtain the following formula:

$$K = \left[\frac{I_R S}{R_{t-1}}\right]\left[\frac{1 - e^{-Kt}}{\frac{R_t}{R_{t-1}} - e^{-Kt}}\right] \qquad (7)$$

Exercise 6

Verify that Equation (6) can be solved algebraically to obtain Equation (7).

2) Infusion discontinued

Note that $I_R = 0$ when infusion is discontinued, so that Equation (6) becomes

$$R_t = R_{t-1} e^{-Kt}$$

Exercise 7

Solve this equation for K. This will give you the formula to determine the elimination rate constant K when infusion has been discontinued.

Using the above information, you can develop your model (hypothesis), the third step of the scientific method. This will provide the basis for the dosage information you provide as a consultant for your patient.

Test the model

You are now ready for the fourth step of the scientific method, test the model. You will need the following information for your patient: sensitivity, S = 0.045 s/IU, baseline WBPTT = 70 seconds. To determine an initial estimate for the elimination rate constant K, the following patient information has been collected from a 4.5-hour dialysis treatment with an initial loading dose of 2000 IU ($D_0 = 2000$) and a continuous infusion rate of 1500 IU/h.

Table 1
Measured Values of WBPTT

Time from Start of Dialysis (hours)	**WBPTT (seconds)**	**Response (seconds)**	**Heparin Infusion (IU/hour)**	**Elimination Rate Constant (per hour)**
0	155		1500	—
1	140		1500	
2	130		1500	
3	125		1500	
4 (Infusion discontinued)	125		1500	
4.5	100		—	

Exercise 8

Complete Table 1 by calculating values of the response and elimination rate constant. The response values at each time t can be determined from Equation (1) written as R = WBPTT – BL, where BL = 70. Note that for t = 1, 2, 3, and 4 you will need to use Equation (7) to calculate values for K. This equation can be solved intrinsically using technology such as a TI-86™ or TI-92™ graphing calculator or a symbolic algebra system such as Derive™ or Maple™. For t = 4.5, you will need to use the formula for K when infusion has been discontinued.

Exercise 9

Calculate the mean value and the standard deviation for K from the values in Table 1. The mean will be used as an initial estimate of K.

You are now ready to determine an individualized heparin dose for your patient's next dialysis treatment.

Exercise 10

Your patient's primary physician has prescribed a WBPTT of 125 seconds for the next dialysis treatment. Use the mathematical model you developed to determine the loading dose and the constant infusion rate. The result of Exercise 9 can be used for the value of the elimination rate constant. Recall that the baseline is still BL = 70.

You have now determined the values of D and I_R to use for the next dialysis treatment for this patient. This process may be repeated once or twice more, depending on how stable the patient is. Thereafter, for relatively stable patients, the modeling procedure need only be repeated once every two or three months. For less stable patients, the procedure may be applied more frequently, depending on the physician's clinical assessment of the patient.

Decide to Retain, Reject or Modify the Model

The fifth step of the scientific method is to make a decision regarding your hypothesis (model). Your action depends on how well the mathematical model actually predicts usable values for patient care. If it does not predict well, you will want to revise the model. You may want to compare your loading dose and infusion rate with those used in common practice. For example, the following facts have been ascertained from statistical analysis of hundreds of dialysis patients.

> Mean loading dose is 1700 ± 500 IU (Range: 500 to 4000 IU)
> Mean infusion rate is 1500 ± 300 IU/h (Range: 600 to 3000 IU/h)
> (The customary statistical usage "mean ± standard deviation" is employed.)

Thesis Defense

You will be asked to give an oral presentation of your model portfolio. This is called the thesis defense. It might help to imagine that you are presenting the results of your research to medical colleagues who have a basic understanding of dialysis. Be sure to include in your defense a discussion of the development of your model as well as the results from applying the model to the specific patient case for which you were a consultant.