Mathematical Modeling of Pharmacokinetic Data

David W. A. Bourne, Ph.D.

Mathematical Modeling of Pharmacokinetic Data

David W. A. Bourne, Ph.D.
College of Pharmacy
Health Sciences Center
Oklahoma University

TECHNOMIC PUBLISHING CO., INC.
LANCASTER · BASEL

Mathematical Modeling of Pharmacokinetic Data

a **TECHNOMIC**® publication

Published in the Western Hemisphere by
Technomic Publishing Company, Inc.
851 New Holland Avenue, Box 3535
Lancaster, Pennsylvania 17604 U.S.A.

Distributed in the Rest of the World by
Technomic Publishing AG
Missionsstrasse 44
CH-4055 Basel, Switzerland

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Main entry under title:
Mathematical Modeling of Pharmacokinetic Data

A Technomic Publishing Company book
Bibliography: p.
Includes index p. 137

Library of Congress Catalog Card No. 94-61269
ISBN No. 1-56676-204-9

MATHEMATICAL MODELING OF PHARMACOKINETIC DATA

HOW TO ORDER THIS BOOK

BY PHONE: 800-233-9936 or 717-291-5609, 8AM–5PM Eastern Time

BY FAX: 717-295-4538

BY MAIL: Order Department
Technomic Publishing Company, Inc.
851 New Holland Avenue, Box 3535
Lancaster, PA 17604, U.S.A.

BY CREDIT CARD: American Express, VISA, MasterCard

For Geoffrey, Katrina, and Aaron

PREFACE

In the field of pharmacokinetics, data analysis seems to be going in different directions. There are many investigators looking at small numbers of data points per subject over many subjects, as in "population analysis." Then there are other investigators taking a minimal approach to modeling using a "noncompartmental approach." The first group is using highly sophisticated techniques to extract pharmacokinetic information about various study populations. In the process some model structure may be ignored. For example, the absorption process present after oral absorption may be left out of the model used in a population analysis because there may be little suitable data to characterize the process. The second group is using mathematically simple techniques to get an overview of drug disposition. This is sometimes done because of the paucity of data or available tools. It has been suggested, inappropriately, that there may not be enough data to perform mathematically modeling analyses so a simple AUC was calculated. In reality, if the data cannot support a modeling approach, the AUC values are not likely to be very accurate.

There is much middle ground that this book hopes to address. There are many well designed studies that can be analyzed using a structured modeling approach. The mathematical tools are available for mainframe and desktop computers. These programs are relatively inexpensive. The hardware to run these programs is also becoming increasingly affordable. The objective of this book is to present a systematic approach to using these tools so that the investigator may extract the maximum information from a given set of data.

This book presents topics that may be included in a one-semester course to advanced undergraduates, graduate students, or professional pharmacy students. Scholars in other fields may also find this material of interest. The

scientist designing or analyzing drug disposition studies may find this book useful. Scientists in other areas may have data that should be modeled. Hopefully, many of the techniques described in this book will be effective.

The book begins with a rationale for mathematical modeling followed by a brief description of the general approach that may be taken. Mathematical models from any field may be analyzed by some of the techniques described in this book, however, a brief review of pharmacokinetic models is presented to provide a common framework for the following chapters. Mathematical models are ultimately expressed as equations. These equations may take different forms, each of which must be calculated appropriately. A major objective is to determine the best estimates of various parameter values. There are a number of techniques for determining initial estimates of these parameters, including graphical methods, linear regression, curve stripping, and area under the curve estimation or deconvolution. Many models found in pharmacokinetics are nonlinear, and thus, nonlinear regression techniques are required for their analysis. Data weighting should be considered. Other topics of a similar nature include extended least squares, Bayesian analysis, and the analysis of population data. Once the results are computed it is necessary to evaluate the tabular, graphical, and statistical output provided by the program. Correct data, correct model specification, appropriate model, and appropriate weighting scheme can all be evaluated by consideration of the program output. The final chapter describes questions of experimental design and covers topics such as pilot study considerations, identifiability of parameter values, and optimal sampling time selection.

These topics have been presented in workshops and seminars as well as to various graduate and professional students. The author would like to thank these participants for their suggestions and feedback. The assistance provided by Steven Strauss and others at Technomic Publishing Company is gratefully acknowledged.

DAVID BOURNE
Oklahoma City, OK

CHAPTER 1

Why Model the Data?

Modeling of data set or sets is not a trivial undertaking. There are many questions that must be answered. What do you want to achieve from the modeling? What type of models do you wish to consider? How good are the data; for each data point, which weighting schemes should be considered? Which is the best model and the best weighting scheme? Have sufficient experiments been performed and if not, what further experiments should be conducted? Finding answers to these questions may take a considerable amount of thought, time, and computer resources. Consequently, one should have good reasons for undertaking the modeling process. Why model the data? Why do we want to use a mathematical model?

A successful model will allow considerable consolidation of the collected data. Experimental results covering pages of tabular data may be represented with a model description and a few parameter values. By going through the process of considering a group of models and selecting a best model, exploration of basic mechanisms becomes possible and may be necessary. Future experiments can be designed more precisely using an appropriate model. Finally, successful determination of a good model and model parameters allows the prediction of future results. Dose calculations rely on the existence of a suitable model.

1.1 CONDENSE THE DATA

Where do we start? Do we collect data to develop the model, or do we use a model to get the best from the data? The analyst may be confronted with a large amount of data that needs to be understood. One logical approach is to analyze the data using appropriate mathematical models, each with a few

TABLE 1.1. Plasma Concentrations Measured after IV Bolus Administration.

Subject #1 Wt: 76 kg Dose 200 mg		Subject #2 Wt: 74 kg Dose 200 mg		Subject #3 Wt: 54 kg Dose 150 mg	
Time (hr)	Concentration (mg/L)	Time (hr)	Concentration (mg/L)	Time (hr)	Concentration (mg/L)
1.0	18.6	1.0	19.3	1.0	19.3
2.0	15.6	2.0	15.8	2.0	14.5
4.0	12.3	4.0	11.5	4.0	12.5
8.0	10.1	8.0	9.8	8.0	10.3
12.0	7.6	12.0	6.5	12.0	6.9
24.0	3.2	24.0	2.1	24.0	3.5
Subject #4 Wt: 58 kg Dose 150 mg		Subject #5 Wt: 94 kg Dose 250 mg		Subject #6 Wt: 82 kg Dose 225 mg	
Time (hr)	Concentration (mg/L)	Time (hr)	Concentration (mg/L)	Time (hr)	Concentration (mg/L)
1.0	18.9	1.0	19.5	1.0	18.7
2.0	14.6	2.0	14.7	2.0	14.9
4.0	12.7	4.0	12.3	4.0	12.3
8.0	10.3	8.0	10.7	8.0	10.3
12.0	7.5	12.0	6.9	12.0	7.9
24.0	3.3	24.0	4.1	24.0	3.5

parameters. Thus many pages of data may be summarized as a model with a small number of parameter values. For example, the data in Table 1.1 may have been collected after a pharmacokinetic study in six subjects. These data were collected after an IV bolus dose to each subject. After plotting the data on semi-log graph paper (Figure 1.1), a one-compartment pharmacokinetic model was selected. This model can be defined in terms of a differential equation [Equation (1.1)] or an integrated equation [Equation (1.2)].

$$\frac{dC}{dt} = -k_{el} \cdot C \qquad C_0 = \frac{\text{dose}}{V} \tag{1.1}$$

$$C = \frac{\text{dose}}{V} \cdot e^{-k_{el} \cdot t} \tag{1.2}$$

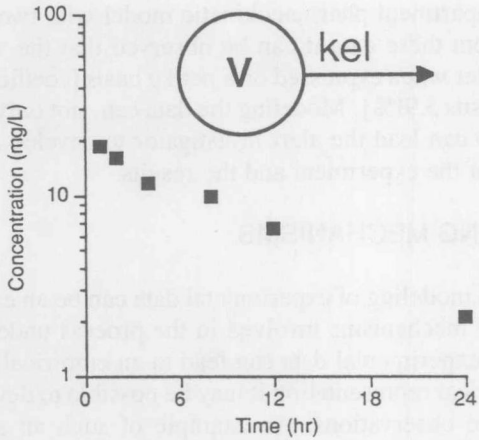

FIGURE 1.1. Data from Subject 1 plotted as a semi-log graph with a diagrammatic representation of a one-compartment pharmacokinetic model.

Nonlinear regression analysis of these data (Bourne, 1989), using a weighting scheme proportional to the reciprocal of the observed data, resulted in the parameter values shown in Table 1.2. Thus, all of the data in Table 1.1 can be represented or summarized as

$$k_{el} = 0.0757 \pm 0.0088 \text{ hr}^{-1}$$

$$V = 10.7 \pm 2.3 \text{ L} = 0.147 \pm 0.006 \text{ L/kg}$$

The data from all six subjects can be condensed since they are consistent

TABLE 1.2. Parameter Values Obtained after Non-Linear Regression Analysis of the Data in Table 1.1.

Subject	Dose (mg)	Wt (kg)	*A* (mg/L)	k_{el} (hr^{-1})	*V* (L)	*V* (L/kg)
1	200	76	18.37	0.07485	10.887	0.1433
2	200	74	19.31	0.09297	10.357	0.1400
3	150	54	18.11	0.07407	8.283	0.1534
4	150	58	18.15	0.07298	8.264	0.1425
5	250	94	17.92	0.06937	13.951	0.1484
6	225	82	17.91	0.06970	12.563	0.1532
Mean				0.0757	10.7	0.147
Std Dev				0.0088	2.3	0.006
CV (%)				11.6	21.3	3.91

with a one-compartment pharmacokinetic model with two parameters, k_{el} and V. Even from these data it can be observed that the variation in V is somewhat smaller when expressed on a per kg basis [coefficient of variation (CV) 21.3% versus 3.91%]. Modeling the data can, not only summarize the results, but also can lead the alert investigator to develop a more detailed understanding of the experiment and the results.

1.2 EXPLORING MECHANISMS

Mathematical modeling of experimental data can be an excellent method of exploring the mechanisms involved in the process under investigation. Analysis of the experimental data can lead to an empirical representation. From this empirical representation it may be possible to develop a theoretical basis for the observations. An example of such an approach is the analysis of the data in Table 1.3. Concentration versus time data from a number of patients was modeled using a one-compartment pharmacokinetic model. The results of this analysis are presented in Table 1.3 along with various patient demographics, including estimates of the patient's creatinine clearance. The linear plot of k_{el} versus CL_{CR}, creatinine clearance (Figure 1.2), indicates that there is a strong linear relationship between these two variables. Thus, a straight line equation [or model, Equation (1.3)] could be used to analyze these data. Thus,

$$k_{el} = a + b \cdot CL_{CR} \tag{1.3}$$

or

$$k_{el} = 0.0355 + 0.00386 \times CL_{CR}$$

This analysis indicates that the drug elimination is dependent on kidney

TABLE 1.3. Parameter Values Obtained in Patients with Various Values of Creatinine Clearance, CL_{CR}.

Subject	Wt (kg)	Sex	CL_{CR} (ml/min)	Dose (mg)	k_{el} (hr^{-1})	V (L)	V (L/kg)
1	75	F	102	200	0.38	15.2	0.203
2	68	F	34	175	0.13	13.2	0.194
3	65	F	21	175	0.10	13.1	0.202
4	98	M	54	250	0.28	19.4	0.198
5	56	M	65	150	0.32	11.2	0.200
6	76	M	76	200	0.36	15.5	0.204
–	–	–	–	–	–	–	–

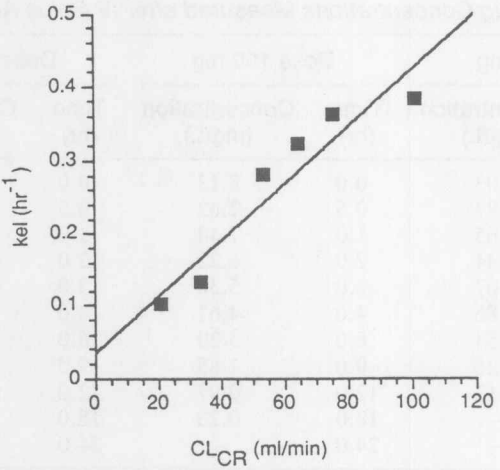

FIGURE 1.2. Plot of elimination rate constant versus creatinine clearance.

function, expressed as the estimate of creatinine clearance. A more complete analysis of the data or a larger sample size might suggest a more complex analysis. Thus modeling the data should give a useful insight into the mechanisms involved. Analysis of the parameter apparent volume of distribution *V* results in a different picture (Figure 1.3). From this plot it appears that the value of *V* is independent of creatinine clearance.

The data in Table 1.4 provides another modeling exercise. These data

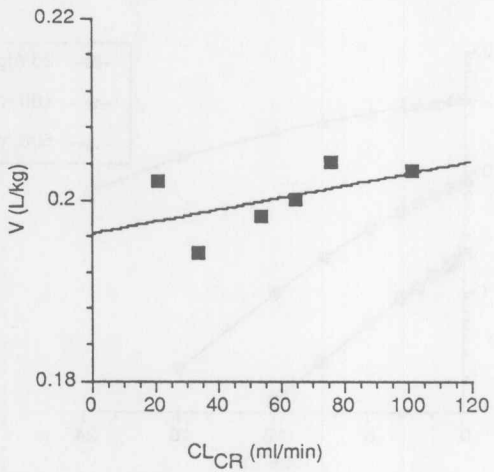

FIGURE 1.3. Plot of apparent volume of distribution versus creatinine clearance.

TABLE 1.4. Drug Concentrations Measured after IV Bolus Administration.

Dose 25 mg		Dose 100 mg		Dose 500 mg	
Time (hr)	Concentration (mg/L)	Time (hr)	Concentration (mg/L)	Time (hr)	Concentration (mg/L)
0.0	2.03	0.0	8.13	0.0	40.6
0.5	1.83	0.5	7.62	0.5	39.8
1.0	1.65	1.0	7.14	1.0	38.9
2.0	1.34	2.0	6.22	2.0	37.2
3.0	1.07	3.0	5.38	3.0	35.6
4.0	0.86	4.0	4.61	4.0	33.9
6.0	0.54	6.0	3.29	6.0	30.7
9.0	0.26	9.0	1.85	9.0	25.9
12.0	0.12	12.0	0.97	12.0	21.4
18.0	–	18.0	0.23	18.0	13.2
24.0	–	24.0	–	24.0	6.6

were collected after three different IV bolus doses. The first step should be to plot the data on semi-log graph paper as shown in Figure 1.4. Examination of this plot indicates a curved line, especially at the higher doses. This strongly suggests that a nonlinear elimination process is involved. Thus, a differential equation such as Equation (1.4) may be appropriate.

$$\frac{dC}{dt} = -\frac{V_m \cdot C}{K_m + C} \qquad C_0 = \frac{\text{dose}}{V} \tag{1.4}$$

The data in Table 1.4 could be modeled using Equation (1.4) to obtain es-

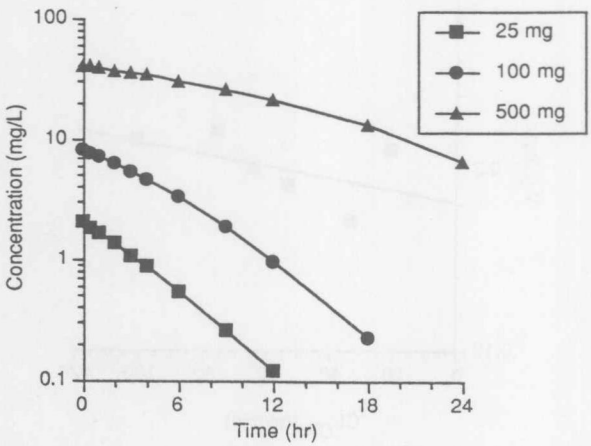

FIGURE 1.4. Plot of drug concentration versus time after various IV bolus doses.

timates of the three parameters V_m, K_m, and V. This analysis will not only condense all the data to a few parameter values, but it will also allow a better understanding of the underlying process.

1.3 MAKING PREDICTIONS

Once we have a mathematical model and suitable parameter values, we can start to use the model to make predictions. For example, we can use a mathematical model [Equation (1.5)] to calculate the dose required to achieve a desired plasma concentration versus time profile. What dose is needed to achieve a plasma concentration of 2 mg/L after 6 hr? If the elimination rate constant and the apparent volume of distribution have been previously determined as 0.13 hr^{-1} and 15 L, respectively, the required dose can be calculated.

$$C = \frac{\text{dose}}{V} \cdot e^{-k_{el} \cdot t} \tag{1.5}$$

$$2 = \frac{\text{dose}}{15} \cdot e^{-0.13 \cdot 6}$$

$$\text{dose} = 65 \text{ mg}$$

A complete concentration versus time profile (out to 6 hr at least) can be calculated with Equation (1.5) using this calculated dose of 65 mg. The results of this calculation are shown in Figure 1.5. An extension of this

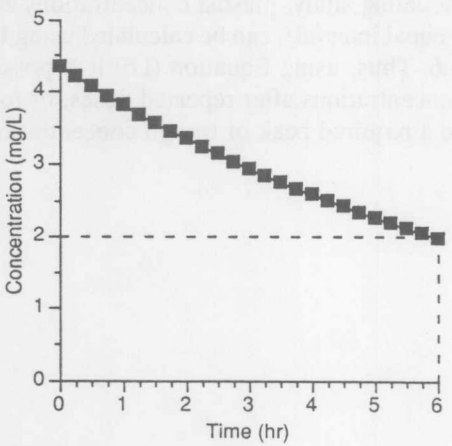

FIGURE 1.5. Plot of drug concentration versus time after a 65 mg IV bolus dose.