DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 15

Pharmacokinetics

Second Edition
Revised and Expanded

Milo Gibaldi
Donald Perrier

Pharmacokinetics

SECOND EDITION, REVISED AND EXPANDED

Milo Gibaldi
University of Washington
School of Pharmacy
Seattle, Washington

Donald Perrier
School of Pharmacy
University of Arizona
Tucson, Arizona

MARCEL DEKKER, INC. New York and Basel

Library of Congress Cataloging in Publication Data

Gibaldi, Milo.
Pharmacokinetics.

(Drugs and the pharmaceutical sciences; v. 15)
Includes bibliographical references and indexes.
1. Pharmacokinetics. I. Perrier, Donald.
II. Title. III. Series. [DNLM: 1. Drugs—Metabolism.
2. Kinetics. W1 DR893B v.14 / QV 38 G437p]
RM301.5.G5 1982 615'.7 82-4608
ISBN 0-8247-1042-8

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Preface

Pharmacokinetics is the study of the time course of drug absorption, distribution, metabolism, and excretion. It also concerns the relationship of these processes to the intensity and time course of pharmacologic (therapeutic and toxicologic) effects of drugs and chemicals. Pharmacokinetics is a quantitative study that requires a preexisting competence in mathematics at least through calculus. It is also a biologic study and can be very useful to the biomedical scientist.

At a fundamental level, pharmacokinetics is a tool to optimize the design of biological experiments with drugs and chemicals. All biologists would benefit from some knowledge of pharmacokinetics whenever they engage in data analysis. It has become increasingly important in the design and development of new drugs and in the reassessment of old drugs. Clinical applications of pharmacokinetics have resulted in improvements in drug utilization and direct benefits to patients.

There is consensus that the origin of pharmacokinetics can be traced to two papers entitled "Kinetics of distribution of substances administered to the body" written by Torsten Teorell and published in the *International Archives of Pharmacodynamics* in 1937. Since this unheralded beginning, the study of pharmacokinetics has matured rapidly; undoubtedly growth has been stimulated by major breakthroughs in analytical chemistry, which permit us to quantitatively detect minute concentrations of drugs and chemicals in exceedingly small volumes of biological fluids, in data processing, and by the brilliant insights of many scientists. Dost, Kruger-Theimer, Nelson, Wagner, Riegelman, and Levy are among those scientists and must be reserved a special place in the history of the development of pharmacokinetics.

Our goals in preparing this revision were similar to those that prompted us to undertake the initial effort. The need for revision was amply clear to us each time we looked at our files, bulging with research papers and commentaries on pharmacokinetic methods and

applications published since 1975. The buzz words today are clearance concepts, noncompartmental models, and physiologic pharmacokinetics. Again, we strived to present the material in an explicit and detailed manner. We continue to believe that *Pharmacokinetics* can be used in formal courses, for self-study, or for reference purposes.

We thank our colleagues for their work and publications, our staffs for their labors and support, and our families for their love and understanding.

Milo Gibaldi
Donald Perrier

Contents

Preface iii

1. One-Compartment Model 1
   Intravenous Injection 2
   Intravenous Infusion 27
   First-Order Absorption 33
   Apparent Zero-Order Absorption 40
   References 42

2. Multicompartment Models 45
   Intravenous Injection 48
   Intravenous Infusion 63
   First-Order Absorption 81
   Determination of Pharmacokinetic Parameters 84
   References 109

3. Multiple Dosing 113
   Intravenous Administration 113
   Intravenous Infusion 128
   First-Order Absorption 132
   Determination of Pharmacokinetic Parameters from Multiple-Dosing Data 143
   References 143

4. Absorption Kinetics and Bioavailability 145
   Absorption Rate 146
   Extent of Absorption 167
   Statistical Considerations in Comparative Bioavailability Studies 185
   Sustained Release 188
   References 195

5. Apparent Volume of Distribution 199
Relationship Between Volume of Distribution, Drug Binding and Elimination, and Anatomic Volume 200
Tissue Binding 209
Estimation of Apparent Volumes of Distribution 211
References 218

6. Kinetics of Pharmacologic Response 221
Kinetics of Directly Reversible Pharmacologic Response 221
Kinetics of Indirect Pharmacologic Response 245
Kinetics of Irreversible Pharmacologic Response 254
Appendix: Solutions for C_S, C_r, and C_T for Cell Systems Sensitive to Drugs That are Cell Cycle Specific 265
References 267

7. Nonlinear Pharmacokinetics 271
Michaelis-Menten Kinetics 271
Some Pharmacokinetic Characteristics of Michaelis-Menten Processes 272
In Vivo Estimation of K_m and V_m 277
Clearance, Half-Life, and Volume of Distribution 287
Drug Concentration at Steady State 289
Time to Steady State 290
Area Under the Curve and Bioavailability 294
Composition of Urinary Excretion Products 297
Other Nonlinear Elimination Processes 301
Enzyme Induction 303
Nonlinear Binding 307
Some Problems in Quantifying Nonlinear Pharmacokinetics 313
References 315

8. Clearance Concepts 319
Organ Clearance 319
Total Clearance 321
Hepatic Clearance 322
Hepatic Clearance and Drug Binding in Blood 327
Drug Binding and Free Drug Concentration 330
Half-Life, Intrinsic Clearance, and Binding 331
First-Pass Effect 332
Gut Wall Clearance 336
Lung Clearance 338
Renal Clearance 341
Clearance Concepts Applied to Metabolites 344
Physical Models of Organ Clearance 347
Blood Clearance Versus Plasma Clearance 349
References 351

9. Physiological Pharmacokinetic Models 355
Blood Flow Rate-Limited Models 358
Experimental Considerations 364
Blood Clearance 366
Lung Clearance 368
Apparent Volume of Distribution 369
Nonlinear Disposition 370
Membrane-Limited Models 372
Species Similarity and Scale-Up 375
References 382

10. Application of Pharmacokinetic Principles 385
Multiple Dosing 385
Dose Adjustments in Renal Failure 393
Hemodialysis 397
Methods for Determination of Individual Patient Parameters 401
References 405

11. Noncompartmental Analysis Based on Statistical Moment Theory 409
Statistical Moments 410
Bioavailability 411
Clearance 411
Half-Life 412
Absorption Kinetics 413
Apparent Volume of Distribution 413
Fraction Metabolized 414
Predicting Steady-State Concentrations 414
Predicting Time to Steady State 415
Conclusions 416
References 416

Appendix A Method of Laplace Transforms 419
References 423

Appendix B Method for Solving Linear Mammillary Models 425
References 431

Appendix C Method of Residuals 433

Appendix D Estimation of Areas 445
Reference 449

Appendix E Prediction of Drug Concentrations on Multiple Dosing Using the Principle of Superposition 451
References 457

Appendix F Estimation of Rates 459
Reference 463

Appendix G Selective Derivations 465
Michaelis-Menten Equation 465
Time To Reach a Fraction of Steady State for a Drug Eliminated by Parallel First-Order and Capacity-Limited Processes 467
Reference 473

Appendix H Computer Programs 475
References 476

Author Index 479
Subject Index 489

1

One-Compartment Model

The most commonly employed approach to the pharmacokinetic characterization of a drug is to represent the body as a system of compartments, even though these compartments usually have no physiologic or anatomic reality, and to assume that the rate of transfer between compartments and the rate of drug elimination from compartments follow first-order or linear kinetics. The one-compartment model, the simplest model, depicts the body as a single, kinetically homogeneous unit. This model is particularly useful for the pharmacokinetic analysis of drugs that distribute relatively rapidly throughout the body. Almost invariably, the plasma or serum is the anatomical reference compartment for the one-compartment model, but we do not assume that the drug concentration in plasma is equal to the concentration of drug in other body fluids or in tissues, for this is rarely the case. Rather, we assume that the rate of change of drug concentration in plasma reflects quantitatively the change in drug concentrations throughout the body. In other words, if we see a 20% decrease in drug concentration in plasma over a certain period of time, we assume that the drug concentrations in kidney, liver, cerebrospinal fluid, and all other fluids and tissues also decrease by 20% during this time..

Drug elimination from the body can and often does occur by several pathways, including urinary and biliary excretion, excretion in expired air, and biotransformation in the liver or other fluids or tissues. Glomerular filtration in the kidneys is clearly a diffusional process, the rate of which can be characterized by first-order kinetics, but tubular secretion in the kidneys, biliary secretion, and biotransformation usually involves enzymatic (active) processes that are capacity limited. However, as demonstrated in subsequent sections of the text dealing with capacity-limited and nonlinear processes (Chap. 7), at low concentrations of drug (i.e., concentrations typically associated with therapeutic doses) the rate of these enzymatic processes can be approximated very well by first-order kinetics. Hence we find

that the elimination of most drugs in humans and animals following therapeutic or nontoxic doses can be characterized as an apparent first-order process (i.e., the rate of elimination of drug from the body at any time is proportional to the amount of drug in the body at that time). The proportionality constant relating the rate and amount is the first-order elimination rate constant. Its units are reciprocal time (i.e., min^{-1} or h^{-1}). The first-order elimination rate constant characterizing the overall elimination of a drug from a one-compartment model is usually written as K and usually represents the sum of two or more rate constants characterizing individual elimination processes:

$$K = k_e + k_m + k'_m + k_b + \cdots \tag{1.1}$$

where k_e and k_b are apparent first-order elimination rate constants for renal and biliary excretion, respectively, and k_m and k'_m are apparent first-order rate constants for two different biotransformation (metabolism) processes. These constants are usually referred to as apparent first-order rate constants to convey the fact that the kinetics only approximate first-order.

INTRAVENOUS INJECTION

Drug Concentrations in the Plasma

Following rapid intravenous injection of a drug that distributes in the body according to a one-compartment model and is eliminated by apparent first-order kinetics, the rate of loss of drug from the body is given by

$$\frac{dX}{dt} = -KX \tag{1.2}$$

where X is the amount of drug in the body at time t after injection. K, as defined above, is the apparent first-order elimination rate constant for the drug. The negative sign indicates that drug is being lost from the body.

To describe the time course of the amount of drug in the body after injection, Eq. (1.2) must be integrated. The method of Laplace transforms in Appendix A will be employed. The transform of (1.2) is

$$s\bar{X} - X_0 = -K\bar{X} \tag{1.3}$$

where X_0 is the amount injected (i.e., the dose) and s is the Laplace operator. Rearrangement of (1.3) yields

$$\bar{X} = \frac{X_0}{s + K} \tag{1.4}$$

which when solved using a table of Laplace transforms (Appendix A) gives

$$X = X_0 e^{-Kt} \tag{1.5}$$

where e represents the base of the natural logarithm. Taking the natural logarithm of both sides of (1.5) gives

$$\ln X = \ln X_0 - Kt \tag{1.6}$$

Then, based on the relationship

$$2.303 \log a = \ln a \tag{1.7}$$

Eq. (1.6) can be converted to common logarithms (base 10, log):

$$\log X = \log X_0 - \frac{Kt}{2.303} \tag{1.8}$$

The body is obviously not homogeneous even if plasma concentration and urinary excretion data can be described by representing the body as a one-compartment model. Drug concentrations in the liver, kidneys, heart, muscle, fat, and other tissues usually differ from one another as well as from the concentration in the plasma. If the relative binding of a drug to components of these tissues and fluids is essentially independent of drug concentration, the ratio of drug concentrations in the various tissues and fluids is constant. Consequently, there will exist a constant relationship between drug concentration in the plasma C and the amount of drug in the body:

$$X = VC \tag{1.9}$$

The proportionality constant V in this equation has the units of volume and is known as the apparent volume of distribution. Despite its name, this constant usually has no direct physiologic meaning and does not refer to a real volume. For example, the apparent volume of distribution of a drug in a 70 kg human can be several hundred liters.

The relationship between plasma concentration and the amount of drug in the body, as expressed by Eq. (1.9), enables the conversion of Eq. (1.8) from an amount-time to a concentration-time relationship:

$$\log C = \log C_0 - \frac{Kt}{2.303} \tag{1.10}$$

where C_0 is the drug concentration in plasma immediately after injection. Equation (1.10) indicates that a plot of log C versus t will be linear under the conditions stated (Fig. 1.1). C_0 may be obtained by extrapolation of the log C versus t plot to time zero. This intercept, C_0, may be used in the calculation of the apparent volume of distribution. Since X_0 equals the amount of drug injected intravenously (i.e., the intravenous dose), V may be estimated from the relationship

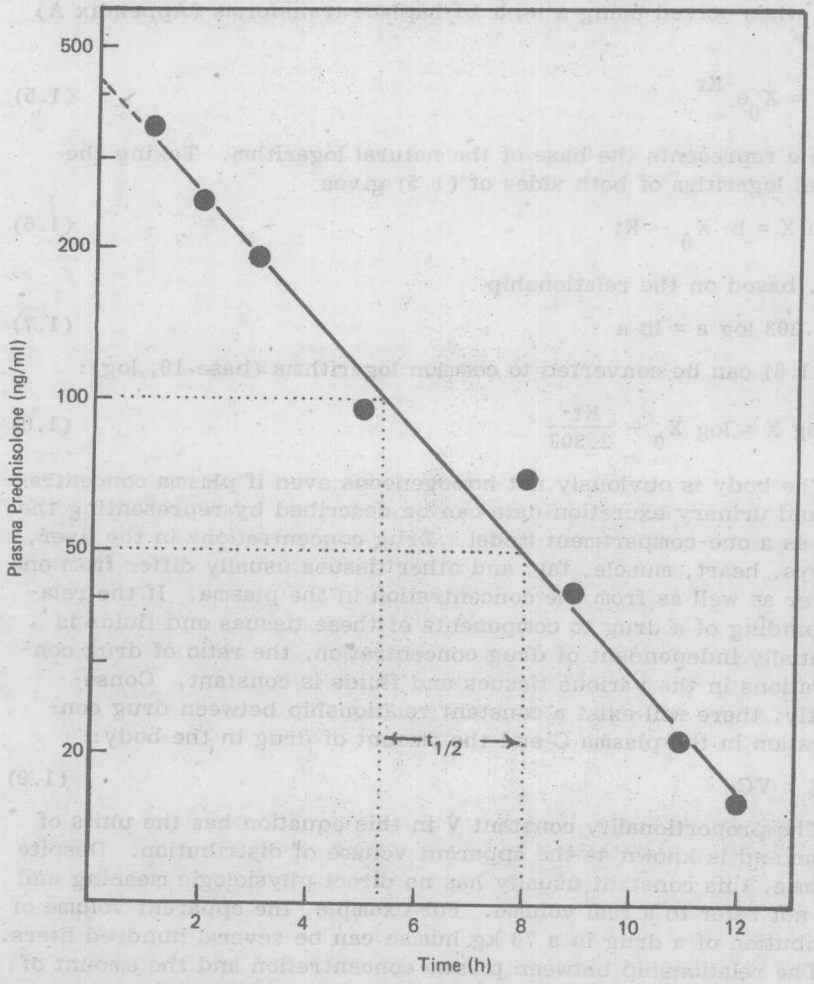


Fig. 1.1 Prednisolone concentration in plasma following an intravenous dose equivalent to 20 mg prednisone to a kidney transplant patient. The data show monoexponential decline that can be described by Eq. (1.10). C_0 = intravenous dose/V; slope = $-K/2.303$. (Data from Ref. 1.)

$$V = \frac{\text{intravenous dose}}{C_0} \qquad (1.11)$$

Equation (1.11) is theoretically correct only for a one-compartment model where instantaneous distribution of drug between plasma and

tissues takes place. Since this is rarely true, a calculation based on Eq. (1.11) will almost always overestimate the apparent volume of distribution. Sometimes the error is trivial, but often the overestimate is substantial and the calculation may be misleading. More accurate and more general methods of estimating V will be discussed subsequently.

The slope of the line resulting from a plot of log C versus time is equal to $-K/2.303$ and K may be estimated directly from this slope. It is easier, however, to estimate K from the relationship

$$K = \frac{0.693}{t_{1/2}} \tag{1.12}$$

where $t_{1/2}$ is the biologic or elimination half-life of the drug. This parameter is readily determined from a semilogarithmic plot of plasma drug concentration (on logarithmic scale) versus time (on linear scale), as illustrated in Fig. 1.1. The time required for the drug concentration at any point on the straight line to decrease by one-half is the biologic half-life. An important characteristic of first-order processes is that the time required for a given concentration to decrease by a given percentage is independent of concentration. Equation (1.12) is easily derived by setting C equal to $C_0/2$ and t equal to $t_{1/2}$ in Eq. (1.10).

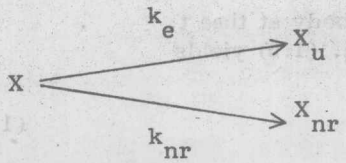
In principle, a plot of the logarithm of tissue drug concentration versus time should also be linear and give exactly the same slope as the plasma concentration-time curve. This is illustrated in Fig. 1.2.

Estimates of C_0, $t_{1/2}$, and K are often obtained from the best straight-line fit (by eye) to the log C versus time data. However, a more objective method is to convert all concentration values to logarithms, and then to determine the best-fitting line by the method of least squares, described in elementary textbooks of statistics [3]. Computer programs are available (see Appendix H) that do not require logarithmic conversions for nonlinear least-squares fitting of data.

Urinary Excretion Data

It is sometimes possible to determine the elimination kinetics of a drug from urinary excretion data. This requires that at least some of the drug be excreted unchanged. Consider a drug eliminated from the body partly by renal excretion and partly by nonrenal processes such as biotransformation and biliary excretion, as shown in Scheme 1,

Scheme 1



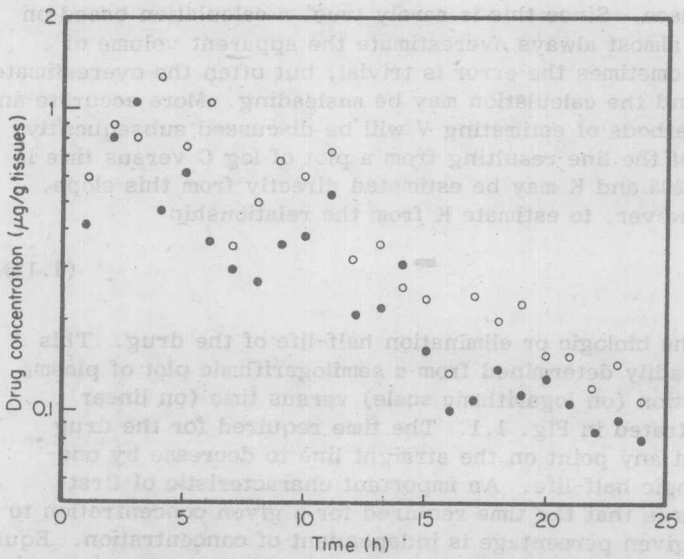


Fig. 1.2 Dipyridamole concentrations in serum (○) and heart tissue (●) after a single oral dose of the drug to guinea pigs. Drug concentrations in serum and heart decline in a parallel manner. (Data from Ref. 2.)

where X_u and X_{nr} are the cumulative amounts of drug eliminated unchanged in the urine and eliminated by all nonrenal pathways, respectively. The elimination rate constant K is the sum of the individual rate constants that characterize the parallel elimination processes. Thus

$$K = k_e + k_{nr} \tag{1.13}$$

where k_e is the apparent first-order rate constant for renal excretion and k_{nr} is the sum of all other apparent first-order rate constants for drug elimination by nonrenal pathways. Since in first-order kinetics, the rate of appearance of intact drug in the urine is proportional to the amount of drug in the body, the excretion rate of unchanged drug, dX_u/dt, can be defined as

$$\frac{dX_u}{dt} = k_e X \tag{1.14}$$

where X is the amount of drug in the body at time t.

Substitution for X according to Eq. (1.5) yields

$$\frac{dX_u}{dt} = k_e X_0 e^{-Kt} \tag{1.15}$$

Therefore,

$$\log \frac{dX_u}{dt} = \log k_e X_0 - \frac{Kt}{2.303} \tag{1.16}$$

Equation (1.16) states that a semilogarithmic plot of excretion rate of unmetabolized drug versus time is linear, with a slope of $-K/2.303$. This slope is the same as that obtained from a semilogarithmic plot of drug concentration in plasma versus time. Thus the elimination rate constant of a drug can be obtained from either plasma concentration or urinary excretion data. It must be emphasized that the slope of the log excretion rate versus time plot is related to the elimination rate constant K, not to the excretion rate constant k_e.

Urinary excretion rates are estimated by collecting all urine for a fixed period of time, determining the concentration of drug in the urine, multiplying the concentration by the volume of urine collected to determine the amount excreted, and dividing the amount excreted by the collection time. These experimentally determined excretion rates are obviously not instantaneous rates (i.e., dX_u/dt) but are average rates over a finite time period (i.e., $\Delta X_u/\Delta t$). However, we often find that the average excretion rate closely approximates the

Table 1.1 Calculation of Excretion Rate Versus Time Data for Estimating Half-Life

t (h)	X_u (mg)	Δt	ΔX_u	$\Delta X_u/\Delta t$ (mg/h)	t_m
0	0.0				
		1	4.0	4.0	0.5
1	4.0				
		1	3.8	3.8	1.5
2	7.8				
		1	3.5	3.5	2.5
3	11.3				
		3	9.1	3.0	4.5
6	20.4				
		6	13.5	2.2	9.0
12	33.9				
		12	14.7	1.2	18.0
24	48.6				
		12	6.4	0.53	30.0
36	55.0				
		12	2.8	0.23	42.0
48	57.8				

Note: The symbols are as follows: t, cumulative time after intravenous administration; X_u, cumulative amount of unmetabolized drug excreted in the urine; Δt, urine collection interval; ΔX_u, amount of drug excreted during each interval; $\Delta X_u/\Delta t$, experimentally determined excretion rate; t_m, midpoint of the collection interval.

instantaneous excretion rate at the midpoint of the urine collection period. The validity of this approximation depends on the collection period relative to the half-life of the drug. An individual collection period should not exceed one biologic half-life and, ideally, should be considerably less. These considerations are discussed in Appendix F. It is important to remember that urinary excretion rates must be plotted against the midpoints of the urine collection periods and not at the beginning or end of these periods (see Table 1.1 and Figs. 1.3 and 1.4).

Fluctuations in the rate of drug elimination are reflected to a high degree in excretion rate plots. At times the data are so scattered that an estimate of the half-life is difficult. To overcome this problem an

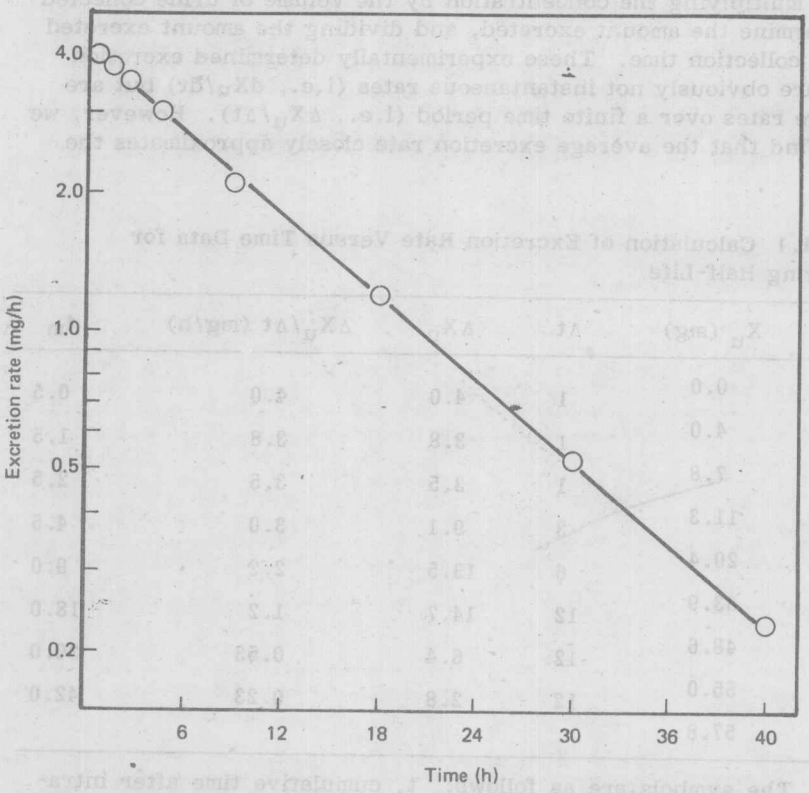


Fig. 1.3 Semilogarithmic plot of excretion rate versus time after intravenous administration of a drug. Data taken from Table 1.1. Each excretion rate is plotted at the midpoint of the urine collection interval. The data are described by Eq. (1.16). Slope = $-K/2.303$.