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Manual of Pharmacologic Calculations

With Computer Programs

With 28 Figures

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Preface

This book provides a collection of quantitative procedures in common use in pharmacology and related disciplines. The procedures we selected may be considered "core" since it is likely that all scientists who work with drugs will use these procedures at some time or another. By excluding very specialized topics, we managed to keep the size of the book small, thus making it handy for quick reference—a handbook in the true sense.

Since many scientists and students now have access to electronic computers, and since the advent of lower cost microcomputers is likely to increase computer availability even further, we also included a computer program for each procedure.* The user need not know computer programming since all necessary information needed to run the programs is included here.

The manual is divided into two parts. In the first, the pharmacologic basis for the calculation is briefly stated for each of the procedures (numbered 1 through 33). Then the appropriate equations (formulas) are given and an example of each calculation is provided. For each procedure, the discussion of theory and illustration of the calculation are brief and self-contained. With the tables in the Appendix and a pocket calculator, all of the calculations can be done without reference to any other source. It is recommended that the procedure and sample calculation be read and understood before going to the automated "magic" of the computer program in Part II. This will ensure an understanding of the theory, particularly the possible limitations of the theory to the data in question.

The computer programs (written in standard BASIC) in Part II are numbered corresponding to their Part I equivalent, prefixed with the code S (programs are

* All computer programs are available on cassette tape or disk. Information on their purchase may be obtained by writing the authors or by referring to the last page of this volume.

also called subroutines). For example, S5 is the program for performing the computations of Procedure 5, *Analysis of the regression line*. All that is necessary is that the desired programs be accurately typed into the computer. Preferably, they should be stored on a disk or tape for loading when they are to be used; the user then need only type RUN and the number of the desired procedure. The computer will ask for the data, which the user types in. The computer then gives the results of the analysis.

For each of the 33 programs in Part II, we give an example of the user's interaction with the computer. The use of the same data in the computer example and in the text example allows the user to relate the knowledge gained in Part I to the use of the computer. The user should actually enter the sample data for a particular program before trying other data, and the results should agree with that given in this book. Erroneous results would indicate that the program was typed in wrong. Details of the computer operation are given in the introduction to Part II.

The authors are grateful to our many friends and colleagues who helped in so many ways in the preparation of this work. We owe special thanks to Alan Cowan, Paul McGonigle, Frank Porreca, Robert Raffa, Mary Jane Robinson, Theresa Tallarida, and Mark Watson for their help with the proof reading and for several valuable suggestions.

Contents

Part I

Computational Procedures

Procedure 1

Dosage and Concentration: Drug Stock Solutions

A drug is to be dissolved in a saline solution in order to make a given volume of specified molarity. If the molarity is denoted by M, the molecular weight by W, and the desired volume by v (ml), then the amount (in grams) of drug is given by

$$G = \frac{MWv}{1000}. \tag{1.1}$$

Isotonic saline (0.009 g/ml) is added to make the volume v.

If the drug is in a concentrated stock solution, the volume of stock solution (in ml) is computed by dividing G by the concentration of stock solution. The concentration of stock solution, denoted by c, is usually expressed either in units of percent (g/100 ml) or in units of g/ml. Hence, the volume of stock needed will be determined by either of the formulas:

for c in units of g/ml

$$x_1 \text{ (ml of stock)} = \frac{MWv}{1000c} = \frac{G}{c} \tag{1.2}$$

for c in units of percent

$$x_2 \text{ (ml of stock)} = \frac{MWv}{10c} = \frac{100G}{c}. \tag{1.3}$$

If the concentration of the final solution is low the drug molecules will not seriously affect the osmolarity of the final solution. However, if the concentration of drug is appreciable and, in particular, if the drug is an electrolyte, the amount of NaCl should be determined in order that the final solution be isotonic with blood. It is necessary, therefore, to find the NaCl equivalent of the grams of drug. The NaCl equivalent of 1 g of drug is first computed. Since the molecular weight of NaCl is 58.5 and since it is 80% dissociated we get the NaCl equivalent of 1 g of drug, denoted by E:

$$E = \frac{58.5}{1.8}\frac{i}{W} = 32.5\frac{i}{W}, \tag{1.4}$$

where i is the dissociation factor of the drug and W is its molecular weight. The dissociation factor for a drug is related to its number of ions and, in the absence of more specific information, may be obtained from Table 1.1.

Table 1.1
Dissociation Factors[a]

Substance	i
nonelectrolyte	1.0
2 ions	1.8
3 ions	2.6
4 ions	3.4
5 ions	4.2

[a] Stoklosa, M. J. *Pharmaceutical Calculations*, Lea and Febiger, Philadelphia, 1974.

Since $G\ (=MWv/1000)$ grams of drug are needed, the NaCl equivalent of this amount is EG. Now the NaCl alone that would be contained in an isotonic solution of volume v (ml) is $0.009v$. Hence, the amount of NaCl (in grams) that is needed is given by Q:

$$Q = 0.009v - EG. \tag{1.5}$$

Water is added to bring the volume to v.

Example

It is desired to make 25 ml of a $10^{-2}\ M$ solution of phenylephrine hydrochloride. A 1% stock solution is to be used. The molecular weight is 204 and the drug dissociates into 2 ions. We have the following:

$$W = 204$$

$$v = 25 \text{ ml}$$

$$M = 0.01$$

$$c = 1\%$$

$$i = 1.8.$$

Equation (1.3) is used to compute the volume of stock solution:

$$x_2 = 0.01 \times 204 \times 25/10$$
$$= 5.1 \text{ ml}.$$

The NaCl equivalent of 1 g of drug is determined from Equation (1.4):

$$E = 32.5 \times 1.8/204$$
$$= 0.29$$

and the amount of NaCl needed for isotonicity is from Equation (1.5):

$$Q = 0.009 \times 25 - 0.29 \times 0.01 \times 204 \times 25/1000$$
$$= 0.21 \text{ g}.$$

Procedure 2

Mean, Standard Deviation, and Confidence Limits

The arithmetic mean is the most commonly used number for describing a set of data from a population or a sample. For the n numbers $x_1, x_2, \ldots, x_n$, in a sample the arithmetic mean, denoted by $\bar{x}$, is given by

$$\bar{x} = \frac{x_1 + x_2 + \cdots + x_n}{n} = \frac{\sum_{i=1}^{n} x_i}{n}. \qquad (2.1)$$

The formula for the mean of a population, denoted μ, is identical to equation (2.1), i.e., $\mu = (\sum_{i=1}^{N} x_i)/N$, where N is the number of items in the population.

The *standard deviation* of a sample of a population measures the dispersion of the set of data about the mean. For a sample having mean $\bar{x}$ the standard deviation s (or $\hat{s}$) is defined by either of the formulas

$$\hat{s} = \sqrt{\frac{\sum_{i=1}^{n} (x_i - \bar{x})^2}{n-1}} \qquad (2.2)$$

or

$$s = \sqrt{\frac{\sum_{i=1}^{n} (x_i - \bar{x})^2}{n}}. \qquad (2.3)$$

For a population having mean μ, the standard deviation σ is defined by

$$\sigma = \sqrt{\frac{\sum_{i=1}^{N} (x_i - \mu)^2}{N}}. \qquad (2.4)$$

Although we measure the sample mean we are really interested in the population mean. For example, we might determine the tension produced in an isolated muscle by a constant drug concentration and make this determination in a sample of muscles. From these values we compute the sample mean $\bar{x}$ as in Equation (2.1). We ask then, to what extent is the sample mean an estimate of the population mean μ? For this purpose we need to specify a confidence level, such as 95% or 99%, and find the upper and lower confidence limits. The confidence limits depend upon the sample size n and the population standard deviation σ. In most research situations, we do not know σ. In such cases the sample standard deviation s (given by Equation 2.3) may be used provided n is sufficiently large, say $n > 30$. The confidence interval, that is, the interval between the confidence limits, is $\bar{x} \pm z \cdot s/\sqrt{n}$. The value of z is that corresponding to an area under the standard normal curve. If the required confidence (or probability) is 95%, then $z = 1.96$ (See Table A.1).

Thus, the 95% confidence limits for the population mean μ are

$$(95\%: n > 30) \qquad \bar{x} \pm 1.96 s/\sqrt{n}. \qquad (2.5)$$

For the 99% confidence interval the value of z is 2.58. Thus,

$$(99\%: n > 30) \quad \bar{x} \pm 2.58s/\sqrt{n}. \tag{2.6}$$

For small samples, $n < 30$, the confidence limits are not determined from the normal distribution. The distribution known as Student's t must be used. Table A.2 gives the values of the area under the distribution curve for various values of t. From Table A.2 we see that the t value requires both the specification of area, 95%, 99%, etc., and the number of degrees of freedom ν. In this application $\nu = n - 1$. Also, the standard deviation used is $\hat{s}$ determined from Equation (2.2). Thus, the confidence interval is computed from

$$\bar{x} \pm t \cdot \hat{s}/\sqrt{n} \tag{2.7}$$

where t has $n - 1$ degrees of freedom.

The expression $(s/\sqrt{n})$ or $(\hat{s}/\sqrt{n})$ is called the *standard error of the mean.*

Example

Measurements of systolic blood pressure were made in a small sample of medical students ($n = 8$) and yielded the following (in mm Hg): 130, 141, 120, 110, 118, 124, 146, 128.

From these data find the mean and sample standard deviation, the standard error of the mean, and the 95% confidence interval of the population mean.

Solution. Application of Equations (2.1) and (2.2) give

$$\bar{x} = 127.$$

$$\hat{s} = 11.9.$$

Hence, std. error $= \hat{s}/\sqrt{n} = 11.9/\sqrt{8} = 4.2.$

The 95% confidence limits are $127 + 4.2t$, where t is determined from Student's t distribution with 7 degrees of freedom. From Table A.2, $t = 2.365$. Thus, the confidence limits are 127 ± 9.97.

Procedure 3

Linear Regression I

Linear regression is a method of curve fitting that is widely used in pharmacology and in other disciplines. The objective is to find a straight line that "best fits" a set of data points (x_i, y_i), $i = 1, \ldots, N$. The usual criterion for defining the best fitting straight line is that the sum of the squares of the vertical deviations from the observed point to the corresponding point on the line is a minimum—a least squares method.

One form of the linear equation is

$$y = mx + b. \tag{3.1}$$

In this equation m is the slope of the line (also called the regression coefficient) and b is the y-intercept. It may be shown that the slope of the regression equation is computed from the equation

$$m = \frac{(\sum x_i)(\sum y_i)/N - \sum (x_i y_i)}{(\sum x_i)^2/N - \sum (x_i)^2}, \tag{3.2}$$

and the y-intercept from

$$b = \bar{y} - m\bar{x}, \tag{3.3}$$

where $\bar{x}$ is the mean x value $= \sum x_i/N$, and $\bar{y}$ is the mean y value $= \sum y_i/N$.

Example

Find the regression line for the points: $(-5, -4), (-1, -2), (3, 4), (5, 6), (8, 7), (10, 10)$, and $(15, 12)$. In this example $N = 7$. The data are most conveniently entered in columns as shown below (Table 3.1).

Table 3.1
Format for Data Entry and Computation

Enter x's	Enter y's	Products	Squares
$x_1 = -5$	$y_1 = -4$	$x_1 y_1 = 20$	$x_1^2 = 25$
$x_2 = -1$	$y_2 = -2$	$x_2 y_2 = 2$	$x_2^2 = 1$
3	4	12	9
5	6	30	25
8	7	56	64
10	10	100	100
$x_N = 15$	$y_N = 12$	$x_N y_N = 180$	$x_N^2 = 225$
$\sum x_i = 35$	$\sum y_i = 33$	$\sum x_i y_i = 400$	$\sum x_i^2 = 449$
$N = 7$			
$(\sum x_i)^2 = 1225$			
$\bar{x} = 5$	$\bar{y} = 4.71$		

The slope is

$$m = \frac{(35)(33)/7 - (400)}{1225/7 - (449)}$$

$$= 0.858,$$

and the y-intercept is

$$b = 4.71 - (0.858)(5)$$

$$= 0.426.$$

The line is shown in Figure 3.1.

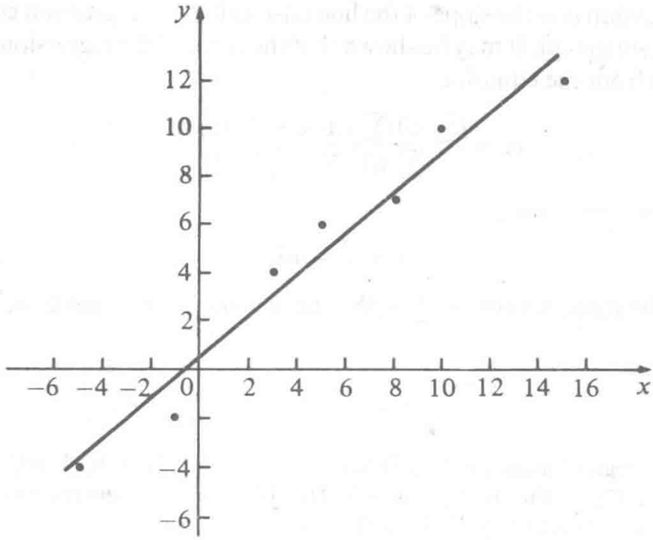

Figure 3.1 Regression line.

Procedure 4

Linear Regression II: Lines through Origin

The general regression line is given by $y = mx + b$ (Procedure 3). If the conditions of a problem require that the regression line go through the origin, then the regression line has the form $y = mx$. There is only one parameter to be determined, namely, the slope m. For this case, the least squares criterion leads to

$$m = \frac{\sum_{i=1}^{n} x_i y_i}{\sum_{i=1}^{n} x_i^2}. \tag{4.1}$$

Example

Find the regression line through the origin for the data given below

x	1	2	3	4	5
y	0.20	0.43	0.55	0.70	0.90

Thus

$$m = \frac{(1)(0.20) + (2)(0.43) + (3)(0.55) + (4)(0.70) + (5)(0.90)}{1^2 + 2^2 + 3^2 + 4^2 + 5^2}$$

$$m = \frac{0.20 + 0.86 + 1.65 + 2.8 + 4.5}{55} = 0.18.$$

The regression line is, therefore, $y = 0.18x$.

Procedure 5

Analysis of the Regression Line

For the regression line $\hat{y} = mx + b$ determined by the points (x_i, y_i), $i = 1, \ldots, N$, the sum of squares about regression SS is given by

$$SS = \sum_{i=1}^{N} (y_i - \hat{y}_i)^2. \tag{5.1}$$

The regression line is found by minimizing SS.

Denoting the mean $\{x_i\}$ by $\bar{x}$, the mean $\{y_i\}$ by $\bar{y}$ and the expression $[SS/(N-2)]^{1/2}$ by s, the estimated standard errors (S.E.) of slope m, y-intercept b, and x-intercept x' are given by the equations below in which each summation is $i = 1$ to N:

$$\text{S.E.}(m) = s\left[\frac{1}{\sum (x_i - \bar{x})^2}\right]^{1/2} \tag{5.2}$$

$$\text{S.E.}(b) = s\left[\frac{1}{N} + \frac{\bar{x}^2}{\sum (x_i - \bar{x})^2}\right]^{1/2} \tag{5.3}$$

$$\text{S.E.}(x')\dagger = \left|\frac{s}{m}\right|\left[\frac{1}{N} + \frac{(\bar{y}/m)^2}{\sum (x_i - \bar{x})^2}\right]^{1/2} \tag{5.4}$$

The confidence intervals for each intercept and for the slope of the regression line are obtained by multiplying the respective estimated standard errors by the appropriate value of Student's t for $N - 2$ degrees of freedom.*

The correlation coefficient r is computed from

$$r = \frac{\sum x_i y_i - N\bar{x}\bar{y}}{\sqrt{(\sum x_i^2 - N\bar{x}^2)(\sum y_i^2 - N\bar{y}^2)}}. \tag{5.5}$$

Example

For the data in the example of Procedure 3 it was found that $y = 0.858x + 0.426$ is the regression equation. The estimated standard errors of intercepts and slope and the correlation coefficient are to be determined. The work is arranged as in the table below (Table 5.1).

† S.E. (x') is symmetric and approximate. See Bliss, *C. I. Statistics in Biology*, P 439. McGraw-Hill, New York, 1967.

* Table A.2.