APPENDIX I

Estimation of Area Under the Curve

There are several methods for estimating the area under a drug concentration-time curve. An estimate of area is required to determine bioavailability, clearance, apparent volume of distribution, and other pharmacokinetic parameters. The most common method of estimating area is the use of the *trapezoidal rule*.

A blood level-time curve can be described by a series of trapezoids that are determined by each concentration-time point (Fig. I–1). The area bounded by the trapezoids approximates the area under the curve; the greater the number of data points, the closer is the approximation.

The area of a trapezoid is equal to one half the product of the sum of the heights times the width. The area under a drug concentration in plasma versus time curve is approximated by the following equation:

$$\text{Area} = (\tfrac{1}{2})(C_1 + C_2)(t_2 - t_1) + (\tfrac{1}{2})(C_2 + C_3)(t_3 - t_2) \ldots + (\tfrac{1}{2})(C_{n-1} + C_n)(t_n - t_{n-1}) \quad \text{(I–1)}$$

where C denotes drug concentration, t denotes time, and the subscript refers to the sample number.

The use of the trapezoidal rule is illustrated in Table I–1. By way of example, the areas of the first, fifth, and seventh trapezoids are calculated as follows:

$$\text{Area (1)} = (\tfrac{1}{2})(0 + 6.6)(1 - 0) = 3.3 \ \mu\text{g-hr/ml} \quad \text{(I–2)}$$

$$\text{Area (5)} = (\tfrac{1}{2})(9.4 + 8.7)(6 - 4) = 18.1 \ \mu\text{g-hr/ml} \quad \text{(I–3)}$$

$$\text{Area (7)} = (\tfrac{1}{2})(6.6 + 3.7)(12 - 8) = 20.6 \ \mu\text{g-hr/ml} \quad \text{(I–4)}$$

The area under the curve from t = 0 to t = 12 hr is the sum of the areas of all trapezoids or 83.3 μg-hr/ml.

Table I–1. Drug Concentration as a Function of Time after Oral Administration

Sample	Time (hr)	Concentration (μg/ml)	Area
1	0	0.0	3.30
2	1	6.6	7.55
3	2	8.5	9.00
4	3	9.5	9.45
5	4	9.4	18.10
6	6	8.7	15.30
7	8	6.6	20.60
8	12	3.7	—
		Total	83.3 (μg/ml per hr)

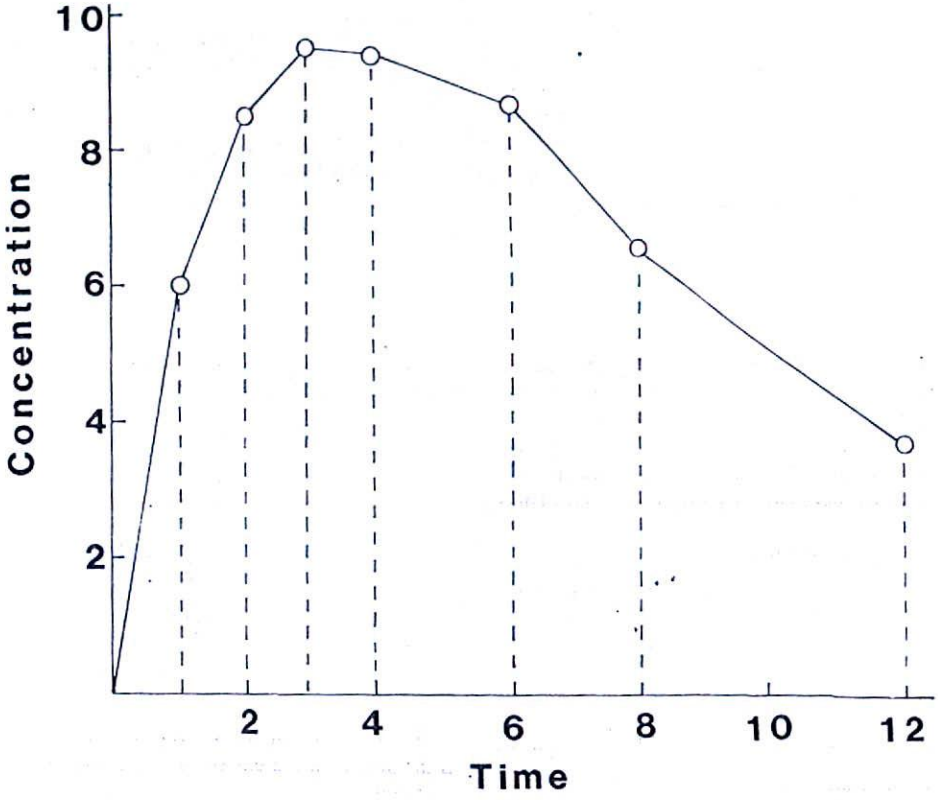

Fig. I–1. Drug concentration (μg/ml) as a function of time (hr) after oral administration. The data points are connected by straight line segments, rather than a smooth curve, to apply the trapezoidal rule. The area of each trapezoid is delineated.

APPENDIX II

Method of Superposition

The method of superposition is a useful noncompartmental approach for predicting drug accumulation and steady-state concentrations on repetitive dosing from data obtained after a single dose. The theoretical basis for superposition is merely that drug concentration is proportional to dose.

The application of superposition to predict the time course of drug concentration under different conditions requires several assumptions. The first is that, irrespective of time of administration, a given single dose administered by a given route will always give rise to the same drug concentration-time curve. A change in dose, but not in route of administration, is reflected by a proportional change in drug concentration at any time after administration. During repetitive administration, blood levels arising from a given dose are simply an additive function of the blood levels associated with that dose and the blood levels resulting from previous doses. This principle is illustrated in Table II–1.

Table II–1 shows how the method of superposition can be used to predict drug concentrations during multiple dosing. In this particular example, drug concentration-time data was obtained after a single dose (see column 2). We wish to predict drug concentrations on repetitive administration of the same dose given every 3 hr. Each subsequent dose, if given independently, would give rise to the same concentrations as the first dose; this is indicated by the values in parentheses. The net concentration after the second, third, or subsequent doses, however, must also reflect the contribution of previous doses.

If given independently, the second dose would provide a drug concentration of 7 μg/ml 1 hr after administration. When given after the first dose, however, the second dose gives rise to a drug concentration of 9.5 μg/ml 1 hr after dosing; 2.5 μg/ml of drug concentration is contributed by the first dose. One hr after giving the third dose, drug concentration equals 9.7 μg/ml (rather than 7 μg/ml) because of the contributions from the two previous doses.

The data in Table I–1 also indicate that steady state is achieved after the third dose, because drug concentrations following the third, fourth, and subsequent doses are identical.

Table II–1. Drug Concentrations (μg/ml) During 4 Consecutive Doses Given at 3-hr Intervals (See Text for Detailed Explanation)

Time	First dose	Second dose		Third dose		Fourth dose	
0	0						
1	7						
2	10						
3	5	(+0)	5				
4	2.5	(+7)	9.5				
5	1.25	(+10)	11.25				
6	0.6	(+5)	5.6	(+0)	5.6		
7	0.2	(+2.5)	2.7	(+7)	9.7		
8	0	(+1.25)	1.25	(+10)	11.25		
9	—	(+0.6)	0.6	(+5)	5.6	(+0)	5.6
10	—	(+0.2)	0.2	(+2.5)	2.7	(+7)	9.7
11	—	(+0)	0	(+1.25)	1.25	(+10)	11.25
12	—	—		(+0.6)	0.6	(+5)	5.6