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Application of the Wagner–Nelson Absorption Method to the Two-Compartment Open Model

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This report considers the application of the Wagner–Nelson method to both one- and two-compartment open model data when there is no competing reaction at the absorption site. Equations are derived which show that application of the Wagner–Nelson method to data which obey the two-compartment open model with first-order absorption allows accurate estimation of not only the rate constant k_a but also the parameters of the two-compartment open model, namely k_{12}, k_{21}, and k_{el}. In the example given, this new method was more accurate than the classical "feathering" or "back-projection" method. The appropriate criterion for "collapsing" the two- to the one-compartment open model is given. In cases where the one-compartment open model applies, and absorption is first order but abruptly ceases after some time, it is shown that k_a may be accurately estimated by application of the Guggenheim method to the A_T/V values calculated for the absorption phase.

KEY WORDS: Wagner–Nelson method; absorption rate constant; one-compartment open model; Loo–Riegelman method; two-compartment open model; competing reactions at absorption site.

INTRODUCTION

The method of Wagner and Nelson (1,2) as originally published, appeared to provide (a) plots of amount of drug absorbed per unit volume of distribution vs. time and (b) plots of percent of drug absorbed vs. time. The method was not designed or claimed to be a method to determine an "absorption rate constant." Wagner and Nelson (1) stated: "When the cumulative percentages absorbed are plotted against time, the resulting plots may contain linear segments; the slope of such a linear segment is the absorption rate in percent/hour. If the plot is curved, or contains curved or

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linear segments, it may often be resolved to yield the components of the rate $d\%A_T/dt$." Notari *et al.* (3), Perrier and Gibaldi (4), and Leeson and Weintraub (5) have discussed problems that arise in estimating "absorption rate constants" when the drug is absorbed and also simultaneously lost to an extravascular compartment via either a parallel first-order or a zero-order process. Loo and Riegelman (6) applied the Wagner–Nelson method (1) to data which obviously obeyed the two-compartment open model with both first-order and zero-order input to the central compartment and stated: "It appears that both the bi-exponential and the occasional appearance of maxima are artifacts of the numerical method."

The method of Loo and Riegelman (6) requires that the drug be administered intravenously before plasma concentration data obtained following oral administration may be evaluated. The method of Wagner and Nelson (1) does not require such intravenous data. Since, intravenous data are frequently not available, the use of the Wagner–Nelson method becomes attractive. It is shown that in the special case where data obey the two-compartment open model with first-order absorption (without a parallel competing reaction), application of the Wagner–Nelson method allows estimation of all the parameters of the two-compartment model.

In resolving Wagner–Nelson "absorption" plots, the original numerical values obtained by the method should be utilized. The values should not be converted to "percentage absorbed" values as originally published (1). This is important since if absorption abruptly ceases because of a "window effect" at the absorption site, the wrong asymptote would be used if the conversion to percentages were made.

THEORETICAL

Relative Magnitude of Asymptotes by Wagner–Nelson (1) and Loo–Riegelman Methods

If it is assumed that data obey the two-compartment open model, then the asymptote obtained by application of the Loo–Riegelman method (6) to the oral data is given by equation 1:

$$A_\infty/V_1 = k_{el}\int_0^\infty C_1(t)\,dt \tag{1}$$

where A_∞ is the amount of drug absorbed to infinite time (which is equal to FD where F is the fraction of the doses, D, which is absorbed), V_1 is the volume of the inner (central) compartment of the two-compartment model shown in Scheme I below, k_{el} is the elimination rate constant, and the integral is the

total area under the plasma concentration–time curve (taken as representative of the area under the concentration–time curve of the central compartment).

Under the same assumptions, the asymptote obtained by application of the Wagner–Nelson method (1) to the oral data is given by equation 2:

$$A_\infty / V_{d_{area}} = \beta \int_0^\infty C_1(t)\, dt \tag{2}$$

In equation 2, $V_{d_{area}}$ and β are given by equations 3 and 4, respectively:

$$V_{d_{area}} = (\alpha/k_{21})V_1 = (k_{el}/\beta)V_1 \tag{3}$$

$$\beta = \tfrac{1}{2}\{(k_{12} + k_{21} + k_{el}) - [(k_{12} + k_{21} + k_{el})^2 - 4k_{21}k_{el}]^{1/2}\} \tag{4}$$

From equations 1, 2, and 3, one obtains the relationship given in equation 5:

$$\frac{\text{Asymptote obtained by Loo–Riegelman method}}{\text{Asymptote obtained by Wagner–Nelson method}} = \alpha/k_{21} = k_{el}/\beta \tag{5}$$

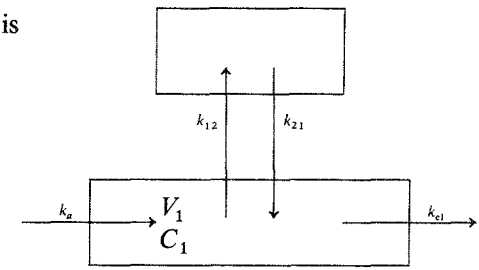
Equation 5 will hold when there is no competing reaction at the absorption site, and for all cases of the two-compartment open model i.e., when absorption is nonuniform, or when absorption obeys uniform kinetics such as first order.

It follows that if one compares two oral treatments (e.g., two different tablets or tablet vs. solution of the drug) and performs only the Wagner–Nelson method, then the ratio of the asymptotes obtained by means of equation 2 is the ratio of the relative amounts of drug absorbed following the two treatments, provided that k_{el}/β remains constant for the subject.

The Two-Compartment Open Model with First-Order Absorption

If data obey this model (shown in Scheme I), then the "K" in the original Wagner–Nelson paper (1) becomes equivalent to "β," as defined by equation 4, since an estimate of "β" is obtained from the terminal oral plasma concentration data.

The model is



Scheme I

For the model shown in Scheme I, C_1 is given by equation 6, where $C_0 = {}^{\text{absorbed}}_{\text{dose}}/V_1$.

$$C_1(t) = k_a C_0 \left[\frac{(k_{21} - \alpha)}{(k_a - \alpha)(\beta - \alpha)} e^{-\alpha t} + \frac{(k_{21} - \beta)}{(k_a - \beta)(\alpha - \beta)} e^{-\beta t} + \frac{(k_{21} - k_a)}{(\alpha - k_a)(\beta - k_a)} e^{-k_a t} \right] \tag{6}$$

By algebraic manipulation it may be shown that

$$F(T) = C_1(T) + \beta \int_0^T C_1(t)\, dt = C_0 \left[\frac{k_{21}}{\alpha} + \frac{1}{\alpha(k_a - \alpha)} \{ k_a(\alpha - k_{21})\, e^{-\alpha T} - \alpha(k_a - k_{21})\, e^{-k_a T} \} \right] \tag{7}$$

A plot of $F(T)$ vs. T is equivalent to a "Wagner–Nelson" plot.[3]

The following is a method for obtaining preliminary estimates of all parameters of the model:

Let A_s = the asymptote of the $F(T),T$ plot. Then

$$A_s = \beta \int_0^\infty C_1(t)\, dt = C_0(k_{21}/\alpha) \tag{8}$$

If $k_a > \alpha > \beta$, and since $\alpha > k_{21}$, equation 7 may be written[4] as

$$F(T) = A_s + I_1\, e^{-\alpha T} - I_2\, e^{-k_a T} \tag{9}$$

where

$$I_1 = C_0 \left\{ \frac{k_a(\alpha - k_{21})}{\alpha(k_a - \alpha)} \right\} \tag{10}$$

and

$$I_2 = C_0 \left\{ \frac{(k_a - k_{21})}{(k_a - \alpha)} \right\} \tag{11}$$

In application of the Wagner–Nelson method, the terminal C_1, t data are fitted to the equation

$$C_1(t) = A_2\, e^{-\beta t} \tag{12}$$

[3]Equation 7 indicates what would be obtained if a Wagner–Nelson calculation (assuming a one-compartment open model) were applied to data generated from equation 6.

[4]The alternative case for $\alpha > k_a > \beta$ is treated in the Appendix.

where

$$A_2 = \frac{k_a C_0(k_{21} - \beta)}{(k_a - \beta)(\alpha - \beta)} \tag{13}$$

After combining equations 8 and 13, one obtains

$$k_a = \frac{\beta A_2(\alpha - \beta)}{(\alpha - \beta)A_2 + \beta C_0 - \alpha A_s} \tag{14}$$

After combining equations 8 and 10, one obtains

$$k_a = \alpha I_1/(I_1 + A_s - C_0) \tag{15}$$

By equating the right-hand sides of equations 14 and 15, one obtains

$$C_0 = \frac{\beta A_2(\alpha - \beta)(I_1 + A_s) + \alpha I_1[\alpha A_s - (\alpha - \beta)A_2]}{\alpha\beta I_1 + \beta A_2(\alpha - \beta)} \tag{16}$$

Rearrangement of equation 8 gives

$$k_{21} = \alpha A_s/C_0 \tag{17}$$

Also,

$$k_{el} = \alpha\beta/k_{21} \tag{18}$$

$$k_{12} = \alpha + \beta - k_{21} - k_{el} \tag{19}$$

The estimates of α and I_1 needed to utilize equations 16–19 are obtained from the least-squares line for $\ln [F(T) - A_s]$,T values where the $F(T)$ values are past the peak of the $F(T)$,T plot. This line is

$$\ln [F(T) - A_s] = \ln I_1 - \alpha T \tag{20}$$

which may be written as

$$[F(T) - A_s] = I_1 e^{-\alpha T} \tag{21}$$

This may be seen from equation 9 where $e^{-k_a T} \simeq 0$. Note also that $F(T)$ is a maximum when $dF(T)/dT = 0$. Differentiating equation 7 gives:

$$\frac{dF(T)}{dT} = -\frac{k_a(\alpha - k_{21})}{(k_a - \alpha)} e^{-\alpha T} + \frac{k_a(k_a - k_{21})}{(k_a - \alpha)} e^{-k_a T} \tag{22}$$

When $dF(T)/dT = 0$, then

$$\frac{k_a(\alpha - k_{21})}{(k_a - \alpha)} e^{-\alpha T_{max}} = \frac{k_a(k_a - k_{21})}{(k_a - \alpha)} e^{-k_a T_{max}} \tag{23}$$

Rearrangement of equation 23, followed by taking natural logarithms of both sides, gives

$$T_{max} = -\frac{1}{(k_a - \alpha)} \ln \left[\frac{\alpha - k_{21}}{k_a - k_{21}} \right] \tag{24}$$

Collapsing of the Two-Compartment Open Model to the One-Compartment Open Model

For the case of bolus intravenous injection, the model shown in Scheme I has no input "k_a step," but rather the dose, D, is introduced into the central compartment at $t = 0$. The equation for C_1 as a function of time in this case is equation 25:

$$C_1(t) = \frac{D}{V_1(\alpha - \beta)} [(k_{21} - \beta) e^{-\beta t} - (k_{21} - \alpha) e^{-\alpha t}] \tag{25}$$

Equation 25 may be written as equation 26:

$$C_1(t) = Ae^{-\alpha t} + Be^{-\beta t} \tag{26}$$

Also,

$$C_1^0 = A + B \tag{27}$$

Hence,

$$C_1/C_1^0 = \{A/(A + B)\} e^{-\alpha t} + \{B/(A + B)\} e^{-\beta t} \tag{28}$$

In the above,

$$A = \frac{D(\alpha - k_{21})}{V_1(\alpha - \beta)} \tag{29}$$

$$B = \frac{D(k_{21} - \beta)}{V_1(\alpha - \beta)} \tag{30}$$

Hence,

$$B/(A + B) = (k_{21} - \beta)/(\alpha - \beta) = V_1/V_{d_{extrap}} \tag{31}$$

where

$$V_{d_{extrap}} = D/B \tag{32}$$

The two-compartment open model "collapses" to the one-compartment open model as $B/(A + B) \to 1$, or as $(k_{21} - \beta)/(\alpha - \beta) \to 1$, or as $V_1 \to V_{d_{extrap}}$. This is also clarified by writing equation 28 as equation 33.

$$C_1/C_1^0 = (1 - V_1/V_{d_{extrap}}) e^{-\alpha t} + (V_1/V_{d_{extrap}}) e^{-\beta t} \tag{33}$$

Hence the ratio α/β is not the determining factor in "collapsing" but rather the relative magnitudes of k_{21}, α, and β, and particularly of k_{21} and α. If

$B/(A + B)$ has a numerical value equal to or greater than about 0.9, then the one-compartment open model will be a reasonable approximation even though the data actually obey the two-compartment open model. The author believes that the two-compartment open model is the actual "minimum" model for linear systems in pharmacokinetics, but under the above conditions the one-compartment open model becomes a good approximation and is useful because of its greater simplicity. In the next section, it is assumed that the one-compartment open model applies; hence K_E replaces β, since when "collapsing" occurs completely then $K_E = k_{el} = \beta$. It should be noted that if "collapsing" occurs, and the Wagner–Nelson method is applied to such data, $F(T)$ will not reach a maximum value and then decrease beyond the maximum, but, instead, the $F(T),T$ plot will slowly approach an asymptote.

Case Where Absorption Abruptly Ceases

Perrier and Gibaldi (4) also considered their "all or none" phenomenon, where drug is being absorbed at a first-order rate from a timed-release or other dosage form, but at some time the drug passes the absorption site and absorption abruptly ceases. They stated that "if the drug is less than fully available due to an all or none phenomenon, the percent of drug absorbed can be calculated relative to the total dose administered rather than relative to the total amount of drug eventually absorbed, A_∞." It is shown in the Experimental and Results section that the Wagner–Nelson method does give the correct bioavailability estimate, and the correct first-order rate constant for absorption in such a case can be calculated without knowing the total amount absorbed per milliliter of the volume of distribution.

EXPERIMENTAL AND RESULTS

Simulation Example No. 1 in Which Equations 6–39 Are Applied

A simulation was performed with $k_a = 2$, $\alpha = 0.5$, $\beta = 0.1$, $k_{21} = 0.25$, and $C_0 = 100$. Using equation 6, one obtains equation 34 for these values of the constants:

$$C_1(t) = 83.3333e^{-0.5t} + 39.4737e^{-0.1t} + 122.8070e^{-2t} \tag{34}$$

Using equation 7, one obtains equation 35:

$$F(T) = 50 + 66.6666e^{-0.5T} - 116.6666e^{-2T} \tag{35}$$

Values of error-free C_1,t and $F(T)$ obtained with equations 34 and 35 are shown in columns 2 and 3, respectively, in Table I. Values of $F(T)$ obtained by applying the Wagner–Nelson method, using the estimated $\beta(\hat{\beta})$ from the terminal C_1,t data and the trapezoidal rule for the areas, are shown in the fifth column of Table I.

Table I. Simulation Example No. 1

	t (hr)	$C_1(T)$	$F(T)$	Trapezoidal area	$\widehat{F(T)}$[a]	$F(T)-A_s = F(T)-50$	$\widehat{F(T)}-\widehat{A_s} = F(T)-50.234$
	0	0	0	0	0		
	0.1	17.804	17.897	0.8902	17.893		
	0.2	31.775	32.118	3.3692	32.112		
	0.4	50.973	52.160	11.6440	52.137		
	0.6	61.921	64.249	22.933	64.214		
	0.8	67.504	71.133	38.876	71.392		
	1.0	69.641	74.646	45.590	74.200		
T_{max} =	1.29726	69.063	76.138	70.206	76.054		
	1.4	68.231	76.011	77.259	76.957		
	1.6	66.075	75.200	90.689	75.144		
	1.8	63.496	73.917	103.646	73.861		
	2.0	60.726	72.388	116.069	72.333		
	2.4	55.140	69.119	139.242	69.064		
	2.8	49.929	66.008	160.256	65.955	16.008	15.721
	3.2	45.284	63.266	179.298	63.214	13.266	12.980
	4.0	37.697	58.983	212.491	58.846	8.983	8.612 } [d]
	6.0	25.812	53.318	276.000	53.412	3.318	3.178
	8.0	19.263	51.221	321.075	51.371	1.221	1.137
	10.0	15.083	50.449	355.421	50.625	0.449	0.391
	12.0	12.096	50.165	383.600	50.456	0.165	0.222
	14.0	9.810	50.061	404.506	50.261		
	16.0	7.998	50.022	422.314	50.229		
	18.0	6.535 } [b]	50.008	436.847	50.220 } [c]		
	20.0	5.346	50.003	448.728	50.219		
	24.0	3.581	50.000	466.582	50.239		

[a] $\widehat{F(T)} = C_1(T) + (\hat{\beta})$ (trapezoidal area).

[b] $\ln C_1 = 3.6915 - 0.100712t$ ($r = -0.99999$) or $C_1 = 40.103e^{-0.10t}$, hence $\hat{\beta} = 0.1$ and $\hat{A}_2 = 40.103$.

[c] $\hat{A}_s$ = average value of $F(T)$ for points used to estimate $\beta = 50.234$.

[d] $\ln[\widehat{F(T)} - \hat{A}_s] = 4.1756 - 0.5051t$($r = -1.0000$) or $\widehat{F(T)} - \hat{A}_s = 65.076e^{-0.5051t}$, hence $\hat{I}_1 = 65.076$ and $\hat{\alpha} = 0.5051$. Only the points which were randomly distributed about the apparent straight line were used—which explains the omission of the last two points.

Table II. Results of Simulation Example No. 1 Using Equations 15–19 Based on the Wagner–Nelson Method

Parameter	Real value	Estimated value	Estimated value calculated with
C_0	100	99.22	Equation 16
α	0.5	0.5051	See footnote *d* of Table I
β	0.1	0.1	See footnote *b* of Table I
k_{12}	0.150	0.152	Equation 19
k_{21}	0.250	0.256	Equation 17
k_{el}	0.200	0.197	Equation 18
k_a	2.00	2.04	Equation 15

Applying equations 15–19 with the constants estimated by the Wagner–Nelson method gave the values shown in column 3 of Table II.

Using the "feathering" or "back-projection" technique, shown in Fig. 1 and Table III, the final equation 36 was obtained. Using equations 36–39 to obtain estimates of C_0 and k_{21}, respectively, and equations 18 and 19 to obtain estimates of k_{el} and k_{12}, respectively, this method gave the results

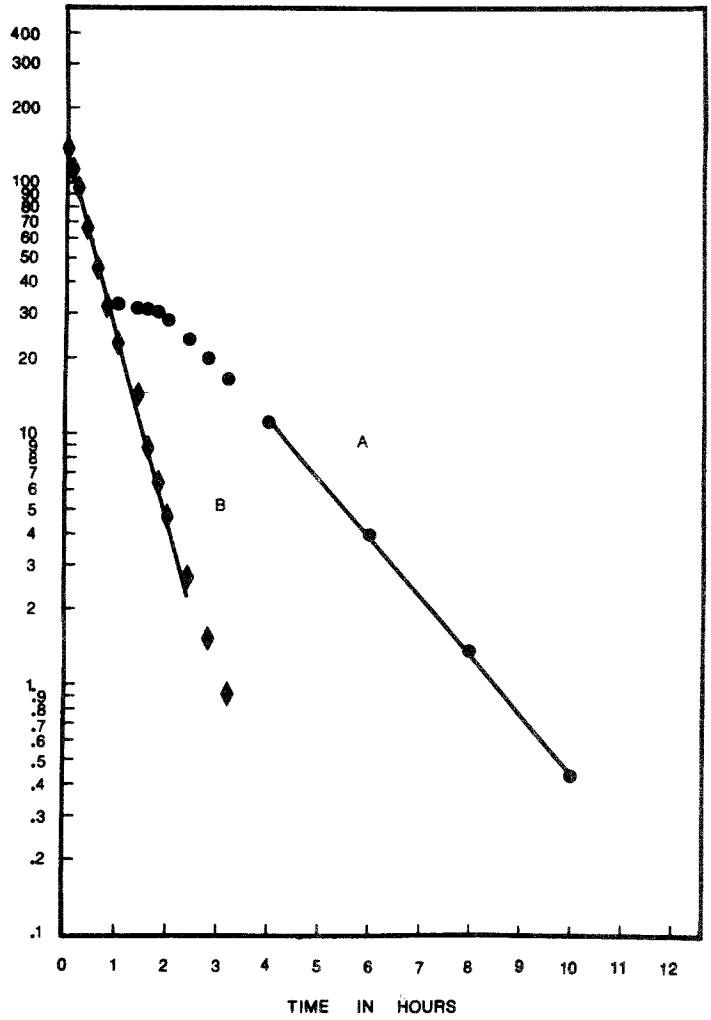


Fig. 1. "Feathering" method used in simulation example No. 1 to obtain equation 36. The line labeled "A" is a plot of R_1, and the line labeled "B" is a plot of R_2. Numerical values and details are given in Table III.

Table III. Estimation of Parameters for Simulation Example No. 1 by "Feathering" or "Back-Projection"

t	C_1	$40.103e^{-0.100712t}$	R_1[a]	$95.34e^{-0.5364t}$	R_2[b]	
0	0	40.103	−40.103	95.34	135.44	
0.1	17.804	39.7010	−21.8971	90.36	112.3	
0.2	31.775	39.3033	−7.5283	85.64	93.17	
0.4	50.973	38.5196	12.4534	76.93	64.48	
0.6	61.921	37.7515	24.1695	69.10	44.93	
0.8	67.504	36.9987	30.5053	62.07	31.56	
1.0	69.641	36.2609	33.3801	55.76	22.38	[c]
1.29726	69.063	35.1914	33.8716	47.54	13.67	
1.4	68.231	34.8291	31.4019	44.99	13.59	
1.6	66.075	34.1346	31.9404	40.42	8.48	
1.8	63.496	33.4539	30.0421	36.30	6.26	
2.0	60.726	32.7868	27.9392	32.61	4.67	
2.4	55.140	31.4923	23.6477	26.31	2.66	
2.8	49.929	30.2488	19.6802	21.23	1.55	
3.2	45.284	29.0545	16.2295	17.13	0.90	
4.0	37.697	26.8054	10.8916	$\ln R_1 = 4.5574 - 0.5364t$		
6.0	25.812	21.9152	3.8968	$(r = -0.9998)$		
8.0	19.263	17.9171	1.3459	or		
10.0	15.083	14.6484	0.4346	$R_1 = 95.34e^{-0.5364t}$		
12.0	12.096	11.9760	0.1200			
14.0	9.810			Hence $\alpha = 0.5364$		
16.0	7.998	$\ln C_1 = 3.6915 - 0.100712t$ $(r = -0.99999)$				
18.0	6.535	or				
20.0	5.346	$C_1 = 40.103e^{-0.100712t}$				
24.0	3.581	Hence $\hat{\beta} = 0.100712$ and $A_2 = 40.103$				

[a] $R_1 = C_1 - 40.103e^{-0.100712t}$.
[b] $R_2 = 95.34e^{-0.5364t} - R_1$.
[c] $\ln R_2 = 4.8354 - 1.651t$ $(r = -0.9988)$, hence $R_2 = 125.89e^{-1.6510t}$.

summarized in Table IV.

$$C_1(t) = 95.34e^{-0.5364t} + 40.103e^{-0.100712t} - 125.89e^{-1.651t} \tag{36}$$

corresponding to

$$C_1(t) = A_1e^{-\alpha t} + A_2e^{-\beta t} - A_3e^{-k_a t} \tag{37}$$

where $A_1 = 95.34$, $A_2 = 40.103$, and $A_3 = 125.89$. Based on these equations, one obtains the estimates of C_0 and k_{21} with equations 38 and 39:

$$C_0 = \frac{A_1(k_a - \alpha) + A_2(k_a - \beta)}{k_a} \tag{38}$$

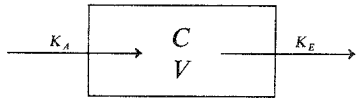
$$k_{21} = \frac{A_1\beta k_a + A_2\alpha k_a + A_3\alpha\beta}{A_1(k_a - \alpha) + A_2(k_a - \beta)} \tag{39}$$

Table IV. Results of Simulation Example No. 1 Using Equations 36–39 Based on "Feathering" or "Back-Projection"

Parameter	Real value	Estimated value	Estimated value calculated with
C_0	100	102.0	Equation 38
α	0.5	0.5364	See Table III and Fig. 1
β	0.1	0.1	See Table III and Fig. 1
k_{12}	0.150	0.169	Equation 19
k_{21}	0.250	0.264	Equation 39
k_{el}	0.200	0.203	Equation 18
k_a	2.00	1.65	See Table III and Fig. 1

It is interesting that the estimated parameters shown in Table II, obtained by the Wagner–Nelson method (at least in this case), are closer to the real values than those obtained via the usual "feathering" or "back-projection" technique shown in Table IV. This is particularly true for the estimate of k_a, where the Wagner–Nelson method gave almost the exact value whereas the "feathering" method gave an estimate that was 17.5% low.

Simulation Example No. 2 for Abrupt Cessation of Absorption



Scheme II

In Scheme II, K_A and K_E are the first-order rate constants for absorption and elimination, respectively. Assume that the model shown in Scheme II applies, and that $A_0/V = 100$ units for one dosage form and 50 units for another dosage form. Assume that $K_A = 1.0455\ \text{hr}^{-1}$ and $K_E = 0.17425\ \text{hr}^{-1}$. Then we can write equations 40 and 41 for the two cases:

$$A_T/V = 100(1 - e^{-1.0455t}) \tag{40}$$

$$A_T/V = 50(1 - e^{-1.0455t}) \tag{41}$$

Let us assume that absorption ceases when 70% of the dose is absorbed. One can then readily calculate that this would occur at 1.15158 hr, and at this time the value of C would be 62.183 units when $A_0/V = 100$ units. In the interval $0 \leq t \leq 1.15158$ hr, C, in the 100-unit case, would be given by equation 42:

$$C = 120(e^{-0.17425t} - e^{-1.0455t}) \tag{42}$$

In the interval $t \geq 1.15158$ hr, C would be given by equation 43 in the 100-unit case:

$$C = (62.183)e^{-0.17425(t-1.15158)} \tag{43}$$

C,t data were generated by use of equations 42 and 43, and analogous equations for the 50-unit case, for various values of t up to 15 hr. Then the Wagner–Nelson method was applied to the simulated data. The results are shown in Table V and the plots of $C_T + K_E \int_0^T C \cdot dt$ vs. T are shown in Fig. 2. From Table V, one can see that the values of the function, $F(T)$, are identical, within the error of the trapezoidal rule and round-off, to the exact values of A_T/V obtained from equations 40 and 41. In Fig. 2, it should be noted that the asymptotes are abruptly reached, rather than approached slowly as would be expected for a completed first-order reaction. Thus, in this case, the asymptotes of approximately 70 and 35 are not the same as the

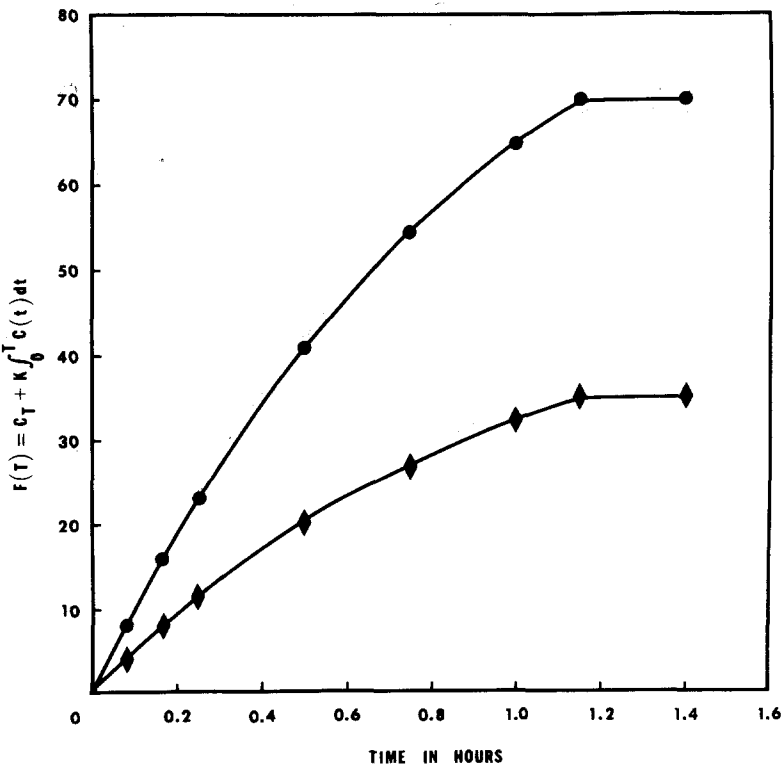


Fig. 2. Application of the Wagner–Nelson method in simulation example No. 2. See details in Table V.

Table V. Application of Wagner–Nelson Method to Simulated Data Where There Is Sudden Cessation of First-Order Absorption

	$C_0 = 100$				$C_0 = 50$			
		$\hat{A}_T/V = C_T$				$\hat{A}_T/V = C_T$		
t	C_T	$\int_0^T C \cdot dt$	$+ K_E \int_0^T C \cdot dt$	$\frac{A_T}{V}$[a]	C_T	$\int_0^T C \cdot dt$	$+ K_E \int_0^T C \cdot dt$	$\frac{A_T}{V}$[b]
0	0	0	0	0	0	0	0	0
0.0833	8.282	0.3451	8.342	8.343	4.141	0.17253	4.171	4.172
0.1666	15.75	1.3463	15.98	15.99	7.875	0.67318	7.992	7.995
0.25	22.49	2.9378	23.00	23.00	11.245	1.4699	11.50	11.50
0.50	38.84	10.61	40.69	40.71	19.42	5.3030	20.34	20.35
0.75	50.52	21.78	54.31	54.35	25.26	10.888	27.16	27.18
1.0	58.63	35.42	64.80	64.85	29.315	17.710	32.40	32.43
1.15158	62.183	44.58	69.95	70.00	31.092	22.288	34.97	35.00
1.4	59.55	59.70	69.95		29.775	29.848	34.975	
2.0	53.64	93.65	69.96		26.82	46.827	34.98	
3.0	45.06	143.0	69.97		22.53	71.502	34.99	
5.0	31.80	219.9	70.11		35.90	109.93	35.05	
7.0	22.44	274.1	70.20		11.22	137.05	35.10	
9.0	15.84	312.4	70.27		7.92	156.19	35.13	
12.0	9.391 [c]	350.2	70.41		4.696 [d]	175.12	35.21	
15.0	5.568	372.7	70.50		2.784	186.33	35.25	
15 to ∞	—	31.96[e]	—		—	15.98[f]	—	
0 to ∞	—	404.7	70.50[g]		—	202.3	35.25[g]	

[a] Calculated from equation 40.

[b] Calculated from equation 41.

[c] Least-squares regression of ln C_T vs. t in the 7- to 15-hr period gave ln $C = 4.3305 - 0.17423t$.

[d] Least-squares regression of ln C_T vs. t in the 7- to 15-hr period gave ln $C = 3.6374 - 0.17423t$.

[e] $\int_{15}^{\infty} C \cdot dt = 5.568/0.17423 = 31.96.$

[f] $\int_{15}^{\infty} C \cdot dt = 2.784/0.17423 = 15.98.$

[g] Value of $0.17423 \int_0^{\infty} C \cdot dt.$

Table VI. Application of the Guggenheim Method (7) to the $\hat{A_T}/V$ Values Shown in Table V

	$C_0 = 100$		$C_0 = 50$	
	$\hat{A_T}/V$	$\Delta(\hat{A_T}/V)^a$	$\hat{A_T}/V$	$\Delta(\hat{A_T}/V)^b$
0	0		0	
		23.00		11.50
0.25	23.00		11.50	
		17.69		8.84
0.50	40.69		20.34	
		13.62		6.82
0.75	54.31		27.16	
		10.49		5.24
1.00	64.80		32.40	

[a]Least-squares regression of $\ln[\Delta(\hat{A_T}/V)]$ vs. t_1 gave

$$\ln[\Delta(\hat{A_T}/V)] = 3.1351 - 1.0467t_1$$

or $\Delta(\hat{A_T}/V) = 22.99e^{-1.0467t_1}$, hence $\hat{k_a} = 1.0467$ (actual value was 1.0455). Hence $\hat{C_0} = 22.99/[1 - e^{-(1.0467)(0.25)}] = 99.9$ (actual value was 100).

[b]Least-squares gave $\ln[\Delta(\hat{A_T}/V)] = 2.4421 - 1.0470t_1$ or

$$\Delta(\hat{A_T}/V) = 11.50e^{-1.047t_1},$$

hence $\hat{k_a} = 1.047$ (actual value was 1.0455). Hence

$$\hat{C_0} = 11.50/[1 - e^{-(1.047)(0.25)}] = 49.9$$

(actual value was 50).

coefficients 100 and 50 of equations 40 and 41, respectively. When one does not know the actual asymptote of a first-order process, one can calculate the rate constant by the method of Guggenheim (7). Application of this method, shown in Table VI, to the A_T/V values at 0, 0.25, 0.5, 0.75, and 1.0 hr gave estimated K_A values of 1.0467 and 1.047 hr^{-1}, which are essentially identical to the actual value of 1.0455^{-1}. Thus the Wagner–Nelson method, followed by appropriate analysis of the A_T/V vs. T plot, gives the correct estimate of the first-order absorption rate constant in the case where absorption abruptly ceases and availability is less than 100%.

Ignoring the shape of the plots shown in Fig. 2, and calculating values of percent remaining unabsorbed by using the asymptotes 70.50 and 35.25 in the denominators when the percentages absorbed are calculated, leads to the same values for both sets of data. These percentages are plotted in Fig. 3. It is obvious that the points form a curved line and that one should not estimate a first-order rate constant from such data. This type of error, where the wrong asymptote is used in estimating a first-order rate constant, was discussed by Wagner (8) in 1963. Thus Perrier and Gibaldi (4) are correct

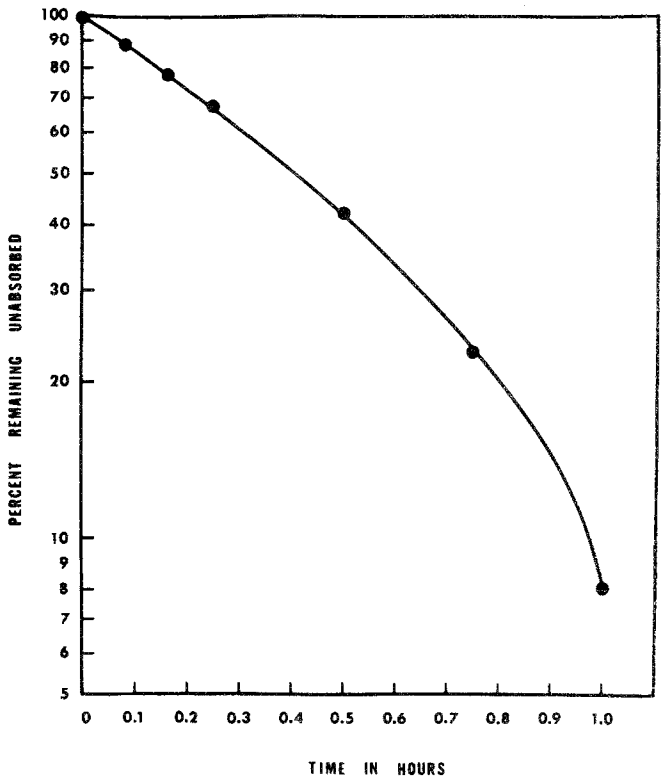


Fig. 3. Plot of percent remaining unabsorbed on logarithmic scale against time when wrong asymptote is used in simulation example No. 2.

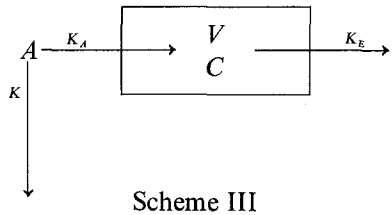
that if one makes this error biased first-order absorption rate constants are obtained. Use of the Guggenheim method, or any alternative method not involving the asymptote, circumvents the problem.

DISCUSSION

The Wagner–Nelson (1) and Loo–Riegelman (6) methods were derived for models not involving competing reactions at the absorption site. The functions obtained by these methods are *exactly* equal to A_T/V or A_T/V_1, respectively, in the case where there is no competing reaction at the absorption site. The functions obtained by these methods are also *exactly* equal to A_T/V or A_T/V_1 respectively, in the case where there is first-order absorption which abruptly ceases after some time and before the entire dose is absorbed. It was shown that in the latter case the correct absorption rate constant may

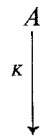
be estimated by applying the Guggenheim method to the A_T/V values rather than the usual σ-minus plot. It must be remembered that the Guggenheim method requires that the A_T/V values be obtained at equally spaced time intervals during the major portion of the absorption phase.

A competing reaction at the absorption site due to chemical degradation of a drug in the gastrointestinal fluids, such as discussed by Notari *et al.* (3), would cause considerable problems in the interpretation of absorption plots obtained by both the Loo–Riegelman (6) and Wagner–Nelson (1) methods. One of the models discussed by Perrier and Gibaldi (4) is shown as Scheme III:

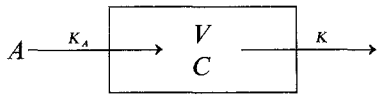


Scheme III

It should be noted that this model assumes that every molecule of A is in solution at $t = 0$, or, after some lag time, t_0, and that all are simultaneously acted on by two first-order processes with rate constants K_A and K. Hence such a model applies to the chemical degradation case as discussed by Notari *et al.* (3). However, the author does not believe that the model shown in Scheme III can be applied to the case where there is an "absorption window" in the upper gastrointestinal tract and the rate constant "K" refers to gastrointestinal transit of the solution of the drug, such as discussed by Perrier and Gibaldi (4). When the rate constant "K" describes the physical process of removal of drug from the absorption site by gastrointestinal transit, we should not write a single model such as shown in Scheme III, but rather sequential models as shown in Schemes IVa and IVb:



Scheme IVa



Scheme IVb

Before the drug reaches the "window" and past the "window," the model shown in Scheme IVa applies. In the window, the model shown in Scheme IVb

applies when the disposition model is the one-compartment open model. In the window, the initial driving force (A_0) would be the amount of drug which has reached the solution state prior to the window. Also, since first-order kinetics are independent of the initial amount or concentration, the same K_A will be measured for a fixed window but different A_0 values. The observed K_A will depend on the size of the window (as it always does), since K_A incorporates the area of the membrane. Thus the problem posed by Perrier and Gibaldi (4) may be overcome by using the consecutive model approach.

APPENDIX

Equation 7 may also be written as equation 7a.

$$F(T) = C_1(T) + \beta \int_0^T C_1(t)\,dt = C_0\left[\frac{k_{21}}{\alpha} + \frac{1}{\alpha(\alpha - k_a)}\{\alpha(k_a - k_{21})e^{-k_aT} - k_a(\alpha - k_{21})e^{-\alpha T}\}\right] \tag{7a}$$

In the following, alternative equations (with numbers followed by "a") replace previous equations with the same numbers (but without the "a") for the case when $\alpha > k_a > \beta$.

$$F(T) = A_s + I_1e^{-k_at} - I_2e^{-\alpha T} \tag{9a}$$

where

$$I_1 = C_0(k_a - k_{21})/(\alpha - k_a) \tag{10a}$$

and

$$I_2 = C_0k_a(\alpha - k_{21})/\alpha(\alpha - k_a) \tag{11a}$$

After combining equations 8 and 10a, one obtains

$$k_a = \alpha(I_1 + A_s)/(C_0 + I_1) \tag{15a}$$

By equating the right-hand sides of equations 14 and 15a, one obtains

$$C_0 = \frac{\beta A_2(\alpha - \beta)I_1 + \{\alpha^2A_s - \alpha(\alpha - \beta)A_2\}\{I_1 + A_s\}}{\alpha\beta(I_1 + A_s) - \beta A_2(\alpha - \beta)} \tag{16a}$$

Equations 8, 12–14, and 17–19 are valid for this alternative case.

Example: Let $k_a = 0.5$, $\alpha = 2$, $\beta = 0.1$, $k_{21} = 0.25$, and $C_0 = 100$. Substitution into equation 6 gives equation 34a:

$$C_1(t) = 20.8333e^{-0.5t} + 9.868421e^{-0.1t} - 30.7018e^{-2t} \tag{34a}$$

Substitution into equations 8, 10a, and 11a gives equation 9b from 9a:

$$F(T) = 12.5 + 16.6666e^{-0.5T} - 29.1666e^{-2T} \quad (9b)$$

Thus $A_2 = 9.868421$, $A_s = 12.5$, and $I_1 = 16.6666$. Substitution of these values into equation 16a yields the expected value of 100 for C_0. It should be noted that in applying the alternative equations above k_a replaces α in equation 20.

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