temperature. Determination of the β-content of the products showed that all preparations had a final β:α ratio of ~1:1 (see Fig. 2). X-ray diffractograms of the samples that were heated to ~200°C proved to correspond to a crystalline β/α-lactose compound.

In conclusion, α-lactose monohydrate is found to lose its water of crystallization and like β-lactose, changes into an amorphous state on intensive grinding. Thermal treatment of both amorphous lactose and uncrystallized α-lactose monohydrate results in crystallization of a crystalline β/α-lactose compound. This is in contrast to uncrystallized β-lactose, which crystallizes into β-lactose.

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Received July 11, 1983.
Accepted for publication March 21, 1984.

Concentration Ratio Method to Determine the Rate Constant for the Special Case when $k_a = k_e$

Keyphrases □ Pharmacokinetics—one-compartment open model, concentration ratio method to determine rate constant

To the Editor:

In a one-compartment open model with first-order absorption and elimination processes, the plasma concentrations (C_p) of a drug at any time, t, after its extravascular administration are generally described by:

$$C_p = \frac{FDk_a(e^{-k_e t} - e^{-k_a t})}{Vd(k_a - k_e)} \qquad \text{(Eq. 1)}$$

where F is the fraction of dose (D) absorbed, k_a and k_e are absorption and elimination rate constants, respectively, and Vd is the apparent volume of distribution. In the special case where k_a is equal to k_e, Eq. 1 becomes mathematically indeterminable, and the general equation (Eq. 2) describing the $C_p t$ profile can be explicitly obtained by setting $k_a = k_e = k$ and using the standard integration technique:

$$C_p = \frac{FDkte^{-kt}}{Vd} \qquad \text{(Eq. 2)}$$

It was proposed recently by Chan and Miller (1) that the $C_p t$ data of this special case could be described by Eq. 1 using the nonlinear regression program NONLIN (2) provided there was at least a small difference between k_a and k_e. This analysis will yield similar values for k_a and k_e which will, in essence, identify equality between k_a and k_e. This approach, applied successfully by the authors to one data set containing 5% random noise, seemed superior to the one proposed by Bialer (3). The shortcomings of the latter were recently discussed by Barzegar-Jalali and Toomanian (4).

In this study, a simple plasma concentration ratio method is proposed to determine the rate constant k using plasma concentrations at any two consecutive times, t_{n-1} and t_n (as defined by Eq. 2):

$$C_p^{n-1} = \frac{FDkt_{n-1}e^{-kt_{n-1}}}{Vd} \qquad \text{(Eq. 3)}$$

and

$$C_p^{n} = \frac{FDkt_{n}e^{-kt_{n}}}{Vd} \qquad \text{(Eq. 4)}$$

Dividing Eq. 4 by Eq. 3, taking the natural logarithm of the resulting expression, and solving for k yields the following relationship:

$$k = \frac{\ln(t_n/t_{n-1}) - \ln(C_p^n/C_p^{n-1})}{(t_n - t_{n-1})} \qquad \text{(Eq. 5)}$$

Where k represents the estimated rate constant between the time interval t_{n-1} to t_n. Since a datum set will usually contain several plasma concentrations, k can be estimated for each time interval and averaged to obtain an overall estimate of k:

$$k = \frac{1}{n-1}\sum_{i=2}^{n}\frac{\ln(t_n/t_{n-1}) - \ln(C_p^n/C_p^{n-1})}{(t_n - t_{n-1})} \qquad \text{(Eq. 6)}$$

It is apparent from Eq. 5 that the proposed method does not require blood sampling at close intervals. Also, the proposed method is applicable to the entire time course of a drug and even to those cases where sampling schedule is limited and regression analysis of the $C_p t$ data according to Eq. 1 is not practical.

The concentration ratio method was compared against the approach of Chan and Miller (1) as well as the theoretical method (Eq. 2). Plasma concentrations with only rounding error were calculated at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, and 16 h using Eq. 2 with $FD/Vd = 10.0$ and $k = 0.5$. Twelve additional datum sets were generated by adding normally distributed random error with an RSD of ±10%. Each set was analyzed by curve-fitting the data to Eqs. 1 and 2 using the NONLIN program as well as by the present concentration ratio method. The curve-fitting of the data to Eqs. 1 and 2 was performed using the reciprocal of plasma concentration as a weighting function. The results are compared in Table I.

The nonlinear regression analysis of the $C_p t$ data according to Eq. 1 identified equality[1] of k_a and k_e in several cases (cases 1, 6–12, Table I). The estimated k_e values by Eq. 1 were smaller (>10%) than that estimated by Eq. 2 in 4 of 14 cases. The mean k_e value estimated by Eq. 1, 0.458, was 8% smaller

[1] Equality was identified when $k_a \pm SD$ overlapped $k_e \pm SD$.

0022-3549/84/0600-0859$01.00/0

Table I—Comparison of Concentration Ratio (Eq. 6) and Nonlinear Regression (NONLIN) Methods for Estimation of Rate Constant for the Special Case of One-Compartment Open Model where $k_a = k_e = k$

Data Set	NONLIN Analysis According to Equation 1 k_a		NONLIN Analysis According to Equation 1 k_e		NONLIN Analysis According to Equation 2 k		Concentration Ratio Method k[a]	
Errorless	0.515	(0.01)[c]	0.485	(0.01)	0.500	(0.0002)	0.499	(0.006)
Errant[b]								
1	0.499	(3.15)	0.495	(3.11)	0.500	(0.009)	0.463	(0.27)
2	0.593	(0.12)	0.430	(0.07)	0.501	(0.01)	0.545	(0.26)
3	0.710	(0.01)	0.387	(0.04)	0.510	(0.01)	0.473	(0.20)
4	0.853	(0.12)	0.349	(0.03)	0.513	(0.02)	0.534	(0.19)
5	0.721	(0.14)	0.377	(0.05)	0.502	(0.02)	0.490	(0.25)
6	0.518	(0.57)	0.474	(0.49)	0.495	(0.02)	0.541	(0.27)
7	0.492	(9.65)	0.489	(9.56)	0.493	(0.02)	0.501	(0.23)
8	0.499	(2.06)	0.485	(1.97)	0.497	(0.02)	0.513	(0.27)
9	0.500	(134)	0.500	(134)	0.501	(0.02)	0.517	(0.29)
10	0.496	(1.38)	0.481	(1.31)	0.498	(0.01)	0.479	(0.27)
11	0.496	(0.96)	0.479	(0.91)	0.479	(0.01)	0.416	(0.39)
12	0.507	(2.68)	0.502	(2.64)	0.504	(0.01)	0.507	(0.21)
Mean	0.570		0.458		0.500		0.498	
SD	0.124		0.057		0.007		0.040	
Mean profile	0.534	(0.01)	0.469	(0.008)	0.500	(0.0004)	0.498	(0.009)

[a] Mean k value (n = 14 time intervals). [b] ±10% Random error as explained in text. [c] Standard deviation (*SD*) in parentheses. The standard deviations reported for parameters estimated by Eqs. 1 and 2 are the standard deviation estimated by NONLIN program whereas the standard deviation obtained from concentration ratio method is the standard deviation of the calculated k values for each interval.

Table II—Comparison of Concentration Ratio and Nonlinear Regression Methods to Data Sets Containing Limited C_p,t Data [a]

Data Set	NONLIN Analysis According to Equation 1 k_a		NONLIN Analysis According to Equation 1 k_e		NONLIN Analysis According to Equation 2 k		Concentration Ratio Method k[b]	
Errorless	0.517	(0.02)[d]	0.484	(0.02)	0.500	(0.0004)	0.500	(0.003)
Errant[c]								
1	0.642	(0.19)	0.412	(0.10)	0.507	(0.02)	0.573	(0.19)
2	0.621	(0.30)	0.416	(0.17)	0.504	(0.02)	0.446	(0.13)
3	0.875	(0.12)	0.355	(0.03)	0.531	(0.02)	0.697	(0.40)
4	1.020	(0.30)	0.319	(0.06)	0.533	(0.04)	0.479	(0.20)
5	0.514	(34.4)	0.513	(34.3)	0.514	(0.02)	0.582	(0.14)
6	0.644	(0.28)	0.398	(0.13)	0.497	(0.02)	0.534	(0.11)
7	0.500	(633)	0.500	(634)	0.500	(0.04)	0.535	(0.17)
8	0.499	(8.05)	0.493	(7.89)	0.500	(0.02)	0.515	(0.20)
9	0.470	(70.7)	0.469	(70.5)	0.468	(0.02)	0.471	(0.15)
10	0.490	(3.20)	0.471	(3.02)	0.484	(0.03)	0.355	(0.29)
11	0.484	(1.72)	0.466	(1.62)	0.478	(0.02)	0.521	(0.10)
12	0.594	(0.24)	0.442	(0.16)	0.509	(0.01)	0.448	(0.17)
Mean	0.613		0.438		0.502		0.513	
SD	0.172		0.060		0.019		0.085	
Mean profile	0.544	(0.02)	0.461	(0.02)	0.500	(0.001)	0.499	(0.005)

[a] Plasma concentration at 0.5, 1, 2, 4, 8, and 12 h only. [b] Mean k value (n = 5 time intervals). [c] ±10% Random error. [d] Standard deviation (*SD*) in parentheses. The standard deviations reported for parameters estimated by Eqs. 1 and 2 are the standard deviation estimated by NONLIN program whereas the standard deviation obtained from concentration ratio method is the standard deviation of the calculated k values for each interval.

Table III—Comparison of Concentration Ratio and Nonlinear Regression (NONLIN) Methods to Data Sets where $k_a > k_e$ by 10% (FD/V_p = 10; k_a = 0.55 and k_e = 0.5)

Data Set	NONLIN Analysis According to Equation 1 k_a		NONLIN Analysis According to Equation 1 k_e		Concentration Ratio Method k[a]	
Errorless	0.525	(3.22)[c]	0.524	(3.22)	0.525	(0.004)
Errant[b]						
1	0.599	(0.17)	0.475	(0.12)	0.527	(0.15)
2	0.599	(0.16)	0.475	(0.11)	0.518	(0.15)
3	0.558	(0.30)	0.500	(0.25)	0.509	(0.15)
4	0.523	(2.31)	0.517	(2.26)	0.521	(0.14)
5	0.517	(4.58)	0.514	(4.54)	0.509	(0.09)
6	0.520	(1.56)	0.510	(1.51)	0.554	(0.20)
7	0.521	(73.1)	0.520	(73.0)	0.530	(0.12)
8	0.525	(4.18)	0.521	(4.13)	0.513	(0.12)
9	0.579	(0.17)	0.478	(0.12)	0.512	(0.12)
10	0.545	(0.35)	0.502	(0.31)	0.494	(0.16)
11	0.591	(0.15)	0.466	(0.10)	0.570	(0.25)
12	0.603	(0.15)	0.465	(0.10)	0.545	(0.15)
Mean	0.557		0.495		0.525	
SD	0.036		0.022		0.022	
Mean profile	0.527	(0.11)	0.522	(0.11)	0.526	(0.007)

[a] Mean k value (n = 14 time intervals). [b] ±10% random error. [c] Standard deviation (*SD*) in parentheses. The standard deviations reported for parameters estimated by Eqs. 1 and 2 are the standard deviation estimated by NONLIN program whereas the standard deviation obtained from concentration ratio method is the standard deviation of the calculated k values for each interval.

than the input value of k_e (0.5) or that estimated by Eq. 2. In contrast, the k values estimated by the concentration ratio method correspond well with those estimated by Eq. 2 (0.5). The concentration ratio method performed adequately when the $C_p t$ data were limited (Table II) and even when k_a was larger than k_e by 10% (Table III).

It must be noted that the nonlinear regression analysis of the $C_p t$ data in terms of Eq. 2 represents the most appropriate method to calculate the rate constant for the special case of the one compartment open model where $k_a = k_e$ (Tables I and II). The pharmacokinetic analysis of the data using Eq. 1 with the NONLIN program is, as suggested by Chan and Miller, the only method known to date to identify the equality between k_a and k_e. The proposed concentration ratio method represents a simple, complimental method which can be applied even in those cases with limited, $C_p t$ data when the model is identified *a priori*.

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Received September 6, 1983.
Accepted for publication April 4, 1984.

OPEN FORUM

Problems Involved with Developing a Suitable Model for Evaluating Exposure to Bis(2-ethylhexyl) Phthalate from Medical Devices

In a recent article, "Effect of Renal Failure and Bis(2-ethylhexyl) Phthalate Pretreatment on the Disposition and Metabolism of Antipyrine in the Rat" [1], Pollack and Shen presented an experimental model for studying chronic exposure of hemodialysis patients to bis(2-ethylhexyl) phthalate (I) [also known as di-2-ethylhexyl phthalate or DEHP]. Their model, however, utilized oral administration (intragastric intubation) of I rather than a parenteral route. Since the authors did not demonstrate that the effects of I upon antipyrine metabolism and disposition were the same when I was administered orally as when it is given parenterally, one must question acceptance of this as a suitable model for evaluating I exposures from hemodialyzers or other medical devices.

A number of reports, including those of Albro and Thomas[2], Rowland[3], and Lake *et al.*[4], indicate that orally administered I leads to absorption primarily of its hydrolytic product, mono-2-ethylhexyl phthalate or MEHP (II). Therefore, the proposed model[1] should be suitable for evaluating exposure to I from food packagings or other oral exposure, but in order for it to be accepted as a suitable model for clinical exposure to I from medical devices it will be necessary to demonstrate that the parameters evaluated are not affected by the route of administration of I.

There is no dispute that I is metabolized *in vivo* to produce II along with other metabolic products. However, the unanswered question in this case is whether or not the diester (I), to which the patient would initially be exposed intravenously during hemodialysis, *etc.*, would produce qualitatively and quantitatively similar effects on antipyrine metabolism and disposition prior to its metabolic conversion, as would the monoester (II) and other metabolic products. A number of reports have indicated differences in biological activity between I and II, or oral *versus* parenteral administration of I. Some of these reported differences include acute LD_{50}[5], *mutagenicity in bacterial systems*[6], *pentobarbital sleeping time* and effects on aminopyrine-*N*-demethylase and aniline hydroxylase[7], and mitochondrial (state 3) respiration[8].

The authors[1] commented on the findings of Agarwal *et al.*[7], that effects on enzyme activities were associated with the route of I administration, but then they dismiss these findings by attributing the differences to doses administered, not route of administration. However, an examination of the data[7] reveal that when an enzyme or biochemical system was affected by oral or parenteral administration of I (*a*) there was generally a dose-related response, and (*b*) comparisons of similar doses (5.2 and 13.0 po *versus* 5.0 and 10.0 ip) often produced markedly different responses.

Thus, because of the various literature reports (a few of which were cited) showing or suggesting a difference in biological activity between I and II or II plus other metabolites, the model proposed to study the effects of I, from artificial kidneys or other medical device exposure, on antipyrine metabolism and disposition cannot be accepted until it is demonstrated that I produces the same effects on these parameters when administered parenterally as when given by gastric intubation.

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Received February 28, 1984.

0022-3549/84/0600-0861$01.00/0