Pharmaceutical Research, Vol. 7, No. 1, 1990

Report

Effects of Variation in Drug Elimination on Five Methods for Assessing Zero-Order Drug Absorption Rates

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Received May 5, 1989; accepted July 11, 1989

The area function method for assessing zero-order (k_o) drug absorption rates was compared to four other methods under conditions where variation occurs in the plasma concentration data and in the elimination rate constant (k_{el} or k_{10}) for one- or two-compartment models. For deviant k_{el} values of a one-compartment model, the most accurate recovery of k_o occurred with the area function method and nonlinear least-squares regression, followed by the Wagner–Nelson and moment analysis methods. With deviant k_{10} values for a two-compartment model, the order of superiority of the methods was: area function ≈ nonlinear regression > Loo–Riegelman > moment analysis. Moment analysis should generally be reserved for use as an estimation rather than calculation technique. The area function procedure offers particular advantages in ease of data analysis and accuracy of recovered parameters.

KEY WORDS: apparent zero-order absorption rate constant; area function analysis; Wagner–Nelson method; nonlinear regression; Loo–Riegelman method; moment analysis; one-compartment model; two-compartment model.

INTRODUCTION

Recently, an area function method was developed to calculate the apparent zero-order absorption rate constant (1). For a zero-order absorption process (k_o) over a duration of time, τ, this method involves calculation of a series of k_o values from

$$k_o = \frac{D \cdot C_{po}(t)}{AUC_{iv}^{0 \to t}} \quad (1)$$

where D is the dose, $C_{po}(t)$ is the plasma concentration at time = t after an oral (po) dose, and $AUC_{iv}^{0 \to t}$ represents the area under the plasma concentration versus time curve following intravenous (iv) dosing measured from time zero to time t. The procedure is independent of the disposition model but requires data following both po and iv dosing. This method is theoretically identical to deconvolution but is more accurate and less sensitive to data variation because of the absence of error-prone consecutive subtraction steps needed in deconvolution (1).

Using simulation data for one- and two-compartment models (1), this method was compared with the Wagner–Nelson method, the Loo–Riegelman method, moment analysis, and nonlinear regression analysis based on the simultaneous fitting of intravenous and oral data to appropriate equations using NONLIN84 (2). It was demonstrated that this method was as accurate as either nonlinear regression analysis or the Wagner-Nelson method and was superior to moment analysis and the Loo–Riegelman method. However, the performance of these methods under conditions of intrasubject variation in drug disposition rates was not evaluated.

Most methods for calculation of absorption rates assume or allow for no intrasubject variability in the kinetics of drug elimination. The effects of using an incorrect elimination rate constant (k_{el}) on the Wagner–Nelson method have been illustrated with computer simulations for theophylline data (3,4) but only limited conditions were evaluated. The comparative sensitivity of the major calculation methods to the use of an incorrect elimination rate constant is still unknown.

The purpose of this communication is (a) to show that the area function method of assessing drug absorption is often equivalent in accuracy to nonlinear regression analysis under various input:disposition conditions and (b) to illustrate that both methods are less sensitive to the use of an incorrect elimination rate constant when compared with the Wagner–Nelson method, the Loo–Riegelman method, and moment analysis. Changes in either k_{el} or k_{10} were assumed to represent primarily intrasubject variation in clearance.

METHODS

Three sets of intravenous and oral plasma concentrations at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, and 32 hr were simulated for a hypothetical drug exhibiting one-compartment model characteristics and the following parameters: D = 300 mg, F = 1, V = 32 liters, k_{el} = 0.10 hr^{-1}, and k_o varied from 25 to 150 mg/hr (i.e., τ = 2–12 hr). Ten

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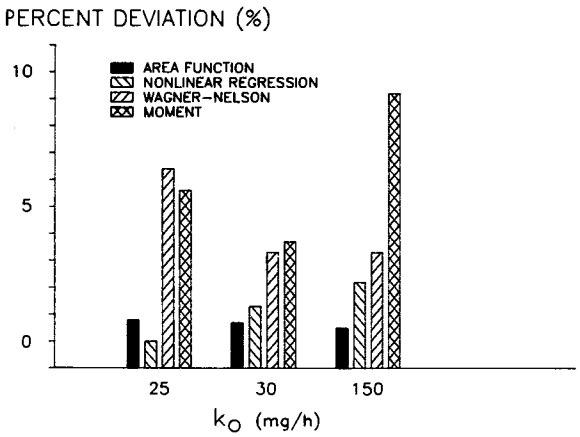

Fig. 1. Comparison of the percentage deviation from the theoretical k_o values obtained by applying the four designated methods to the errant data of the one-compartment model.

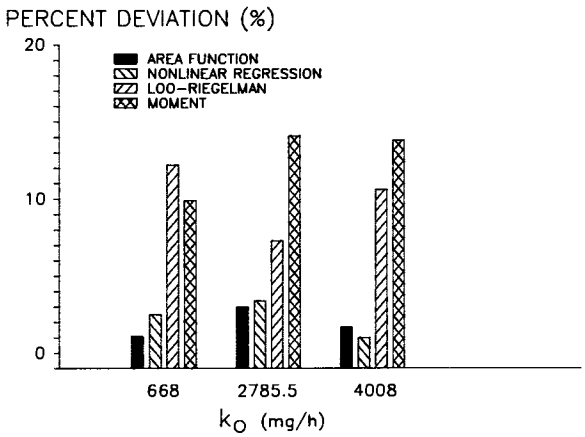

Fig. 2. Comparison of the percentage deviation from the theoretical k_o values obtained by applying the four designated methods to the errant data of the two-compartment model.

additional errant data sets were then generated by adding normally distributed random error with a relative standard deviation of 10% to each concentration. In addition, six errorless intravenous profiles were also generated by changing k_{el} from 0.10 to 0.09 and 0.11 hr^{-1}, while keeping the rest of the parameters unchanged. Similarly, 3 sets of errorless data and 30 sets of errant data at time 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 12, 24, and 48 hr were generated for a hypothetical drug following a two-compartment model with D = 2505 mg, F = 0.8, V_1 = 7.72 liters, k_{12} = 0.45 hr^{-1}, k_{21} = 0.87 hr^{-1}, k_{10} = 0.20 hr^{-1}, and k_o = 668 to 4008 mg/hr (i.e., τ = 0.5–3 hr). Six additional errorless intravenous profiles were also generated by using the same parameters except k_{10} = 0.18 and 0.22 hr^{-1}. These data were then analyzed by the area function method, nonlinear regression analysis, moment analysis, the Wagner–Nelson method (one-compartment model data only), and the Loo–Riegelman method (two-compartment model data only). Values of fractional absorption at time $t[F_a(t)]$ were also calculated by the area function method, by the Wagner–Nelson method, and by the Loo–Riegelman method and were analyzed by linear regression analysis.

RESULTS AND DISCUSSION

The results of the simulation study with random error in the plasma concentration data for a hypothetical drug exhibiting one-compartment model characteristics are summarized in Fig. 1. When applied to both errorless (not shown) and errant data, all of the methods were generally adequate, as values of k_o obtained were within 11% of the true values. However, moment analysis was the least accurate method among these four techniques, while the area function and nonlinear regression methods yielded nearly perfect k_o values.

Values of $F_a(t)$ obtained at various times by the area function and Wagner–Nelson methods using the same data sets were analyzed by linear regression analysis. Data in Table I indicate that both methods gave accurate estimates of $F_a(t)$ values. The results were very close to the theoretical values of $F_a(t)$ with slopes = $1/\tau$, correlation coefficients of essential unity, and intercepts of essential zero.

When applied to errorless data (not shown) for a hypothetical drug showing two-compartment model characteristics, the area function method and nonlinear regression anal-

Table I. Linear Regression Analysis of $F_a(t)$ Data Obtained from a One-Compartment Model by Two Calculation Methods

k_o (mg/hr)	$1/\tau$ (hr^{-1})	Data variation	Area function			Wagner–Nelson		
			Slope	Intercept	r	Slope	Intercept	r
25.0	0.083	Errorless	0.0833 (0)[a]	0.0006	1.0000	0.0827 (0.7)	0.0002	1.0000
		Errant	0.0842 (1.1)	−0.0014	0.9990	0.0880 (5.6)	0.0098	0.9996
30.0	0.10	Errorless	0.0998 (0.2)	0.0003	1.0000	0.0993 (0.7)	0.0001	1.0000
		Errant	0.0984 (1.6)	0.0052	0.9997	0.0988 (1.2)	0.0070	0.9998
150.0	0.50	Errorless	0.500 (0)	−0.0010	1.0000	0.497 (0.6)	0	1.0000
		Errant	0.487 (2.6)	0.012	1.0000	0.483 (3.4)	0.011	1.0000

[a] Number in parentheses is the absolute value of the percentage deviation from the theoretical value.

Table II. Linear Regression Analysis of $F_a(t)$ Data Obtained from a Two-Compartment Model by Two Calculation Methods

k_o (mg/hr)	$1/\tau$ (hr^{-1})	Data variation	Area function			Loo–Riegelman		
			Slope	Intercept	r	Slope	Intercept	r
668	0.33	Errorless	0.332 (0.3)[a]	0.00008	1.0000	0.307 (7.9)	0.0003	1.0000
		Errant	0.309 (7.2)	0.021	0.9980	0.293 (12.0)	0.012	0.9989
2785.5	1.39	Errorless	1.384 (0.5)	0.0004	1.0000	1.292 (7.1)	−0.00004	1.0000
		Errant	1.417 (1.9)	−0.007	0.9996	1.306 (6.1)	−0.004	0.9997
4008	2.00	Errorless	1.996 (0.2)	−0.001	1.0000	1.864 (6.8)	−0.002	1.0000
		Errant	2.032 (1.6)	0.019	1.0000	1.860 (7.0)	0.007	1.0000

[a] Number in parentheses is the absolute value of the percentage deviation from the theoretical value.

ysis yielded correct estimates for k_o. The Loo–Riegelman method and moment analysis also performed satisfactorily but were less accurate. When applied to errant plasma concentration data (Fig. 2), the area function method and nonlinear regression analysis performed very well and were superior to the Loo–Riegelman method and moment analysis. Inaccurate estimation of absorption rate constants by the latter two methods under similar conditions has been reported previously (5,6). However, it has been shown that such estimates by these two methods could be improved by assessing concentrations more frequently in the absorption phase (6).

The results of linear regression analysis on $F_a(t)$ values obtained by the area function method and the Loo–Riegelman method are listed in Table II. The area function method performed consistently better than the Loo–Riegelman method in yielding slopes which are closer estimates of $1/\tau$, but the maximum error for the latter was only 12%.

The kinetics of absorption were assessed using intravenous dose data exhibiting ±10% difference in elimination rate constant (k_{el}) from the oral dose data of a drug obeying a one-compartment model as shown in Table III. The error in the k_o calculated by either the area function method or nonlinear regression analysis was within ±3.1%. This error was two- to threefold greater with the Wagner–Nelson method and at least five times larger when moment analysis was applied. Similar findings with the Wagner–Nelson method have been reported previously (3,4). For similar reasons, Wagner (3) recommends use of the terminal rate constant from the same profile used for assessing drug absorption rates.

The effects of ±10% intrasubject variation in the elimination rate constant (k_{10}) on k_o estimates by four methods were also illustrated using data generated for a hypothetical drug exhibiting two-compartment model characteristics. As indicated in Table IV, the area function method and nonlinear regression analysis were practically insensitive to the assigned perturbations in k_{10}. The Loo–Riegelman method gave the second largest percentage error in estimating k_o. Moment analysis sometimes produced extremely aberrant values of k_o and was clearly an unreliable method. This procedure should thus be employed primarily to obtain starting estimates for subsequent application of nonlinear regression analysis.

In summary, the preceding exercise in data analysis in-

Table III. Effects of 10% Variation in k_{el} on Values of k_o Calculated by Four Methods for One-Compartmental Model Data

Input value		Percentage error in k_o			
k_{el} (hr^{-1})	k_o (mg/hr)	Area function	Nonlinear regression	Wagner–Nelson	Moment method
0.09	25	−2.8	+2.0	+4.5	+22.4
0.10	25	0	0	−0.8	−0.4
0.11	25	+2.4	−1.6	−4.8	−13.4
0.09	30	−2.3	+2.3	+5.8	+38.5
0.10	30	−0.4	0	+0.8	−0.4
0.11	30	+2.0	−1.0	−5.7	−15.7
0.09	150	−0.7	+3.1	+8.4	—[a]
0.10	150	0	0	−0.6	−1.4
0.11	150	+0.6	−1.5	−8.0	−48.0

[a] A negative value of k_o prevented calculation of k_o.

Table IV. Effects of 10% Variation in k_{10} on Values of k_o Calculated by Four Methods for Two-Compartmental Model Data

Input value		Percentage error in k_o			
k_{10} (hr^{-1})	k_o (mg/hr)	Area function	Nonlinear regression	Loo–Riegelman	Moment method
0.18	668	−1.4	−1.7	−0.3	+208.9
0.20	668	−0.4	−0.01	−8.0	+7.1
0.22	668	+0.7	+1.6	−14.8	−6.1
0.18	2785.5	−0.8	−1.3	+2.5	—[a]
0.20	2785.5	−0.4	−0.01	−7.2	+8.5
0.22	2785.5	+0.05	+1.0	−14.8	−53.3
0.18	4008	−0.7	−1.5	+2.6	—[a]
0.20	4008	−0.3	+0.01	−7.0	−3.5
0.22	4008	+0.01	+1.1	−14.9	−63.8

[a] A negative value of k_o prevented calculation of k_o.

dicated that the area function method of assessing drug absorption rates for suitable models gave estimates of k_o which were generally as accurate as nonlinear regression analysis and the Wagner–Nelson method where the data contained random error. The method is far superior to the Loo–Riegelman method and moment analysis. In addition, this method and the Wagner–Nelson method were adequate to calculate fractional absorption with time, whereas the Loo–Riegelman method was less accurate. The area function method and nonlinear regression analysis were less sensitive to the use of incorrect elimination rate constants compared with the other methods. Although the assigned error was only ±10%, the comparisons allow assessments of relative merits of the various techniques and raise particular concerns about use of the moment method. In the context of allowing direct analysis of experimental data without the need for a more complex model assignment or the specification of oral and iv equations as required in use of NONLIN analysis, the area function method offers both accuracy and ease of application. However, as pointed out previously (1), the area function methods require assessment of the absorption kinetics to allow selection of the appropriate equations for calculation of zero-order (1) versus first-order (7) absorption rates. An easy method to do this is to assume that constant absorption occurs over each time interval and to employ Eq. (19) from Ref. 1 to calculate a series of absorption rates to plot versus time. Zero-order processes produce absorption rates that fluctuate about a constant value, while first-order absorption produces a declining step function (1).

ACKNOWLEDGMENTS

This work was partly supported by NIH Grant 41037 from the National Institute of General Medical Sciences, National Institutes of Health.

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