The Impact of Lag Time on the Estimation of Pharmacokinetic Parameters. I. One-Compartment Open Model

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Lag time in pharmacokinetics corresponds to the finite time taken for a drug to appear in systemic circulation following extravascular administration. Lag time is a reflection of the processes associated with the absorption phase such as drug dissolution and/or release from the delivery system and drug migration to the absorbing surface. Failure to specify the lag time can lead to inappropriate or erroneous estimates of pharmacokinetic parameters. This has been demonstrated in the case of a one-compartment open model by the pharmacokinetic analysis of bioequivalence data from a study involving the administration of propoxyphene napsylate to human volunteers. Subsequently, pharmacokinetic and statistical analyses of data obtained from a series of 49 simulations involving a wide range of absorption and elimination rate constants (0.05 to 5.00 and 0.01 to 0.95 hr^{-1}, respectively) showed that lag time has a substantial effect on several primary and secondary pharmacokinetic parameters.

KEY WORDS: lag time; pharmacokinetics; PCNONLIN; absorption rate constant.

INTRODUCTION

Pharmacokinetics involves the mathematical characterization of the processes of drug absorption, distribution, excretion, and biotransformation. Mathematical modeling offers a practical way to represent quantitative data and allows the consideration of an array of interrelated variables. To model a set of pharmacokinetic data effectively, complex rate equations must be solved for estimates of parameters involved in the model. For example, in the equation for a typical one-compartment open model with extravascular administration,

$$C(t) = \frac{F \cdot D}{V} \frac{K_a}{K_a - K_{el}} (e^{-K_{el}t} - e^{-K_a t}) \quad (1)$$

where $C(t)$ is the drug concentration in blood/plasma at time t, D is the dose of drug administered, F is the fraction of dose absorbed, K_a is the rate constant of absorption, K_{el} is the rate constant of elimination, and t is the elapsed time [$0 \leq t \leq \infty$], there are at least three primary parameters to be estimated: K_a, K_{el}, and F/V. Based on these primary parameters, several other secondary parameters, such as AUC, half-lives of absorption and elimination, clearance, time to reach peak drug concentration (t_{max}), and peak drug concentration (C_{max}), can be estimated.

An inherent assumption in Eq. (1) is that $K_a \gg K_{el}$. A peculiar problem arises with this one-compartment open model when the rate constants are approximately equal. In such a case, Eq. (1) can be modified to the following:

$$C(t) = \frac{F \cdot D}{V} K \cdot t \cdot e^{-Kt} \quad (2)$$

where $K_a = K_{el} = K$.

It is mathematically reasonable to have a situation wherein the rate constants are numerically equal, but there does not appear to be any evidence in the literature attesting to the occurrence of this phenomenon. Nonetheless, recent reports have discussed the mathematical basis of such a model [Eq. (2)] in considerable detail but have failed to describe the biopharmaceutic relevance of such a model (2–9). In fact, the phenomenon of "equal rate constants" could well arise as a result of any of the following situations, each of which could result in a reduction of the apparent K_a such that $K_a \approx K_{el}$: (i) administration of a slowly dissolving drug; (ii) alterations in the gastric emptying rate; (iii) the presence of food or other interactants in the gastrointestinal tract; (iv) the use of a dosage form with sustained or controlled release characteristics; (v) altered rate and extent of blood perfusion at the absorption site; or (vi) *inappropriate modeling* (inclusion or exclusion of important parameters).

One pharmacokinetic parameter often ignored in the evaluation of a drug is lag time. The authors' serendipitous experience in the course of the evaluation of a set of bioequivalence data, as described in this paper, demonstrates that lag time has a significant effect on the analysis of plasma drug concentration–time data. Ignoring lag time by assuming that it has no significant effect on the outcome could lead to an aberration in the modeling and evaluation of data. The focus of this study, then, is to establish the impact and importance of lag time in pharmacokinetic modeling.

Lag time is generally defined as the delay between drug administration and its systemic appearance or detection in blood or urine (10–16). Lag time may be the result of delayed release of drug from the dosage form and/or of negligible absorption at the site of administration. Lag times are often encountered upon peroral drug administration due to slow disintegration and/or dissolution of solid dosage forms (e.g., tablets, capsules). Typically, long lag times are observed following ingestion of enteric-coated tablets due to the delay in gastric emptying and the time taken for the protective layer to dissolve, erode, or swell prior to drug release from the core formulation.

Lag time actually corresponds to a lag phase which is a reflection of many microprocesses occurring during the absorption phase such as (i) *dispersal* or *disintegration* of the delivery system; (ii) drug *dissolution* and/or *release* from the delivery system; (iii) *transit* of monolith and particulate components to and from absorption site(s); (iv) molecular *migration* to the absorbing surface; (v) molecular *transfer* through the absorbing site tissues; and/or (vi) negligible drug absorption from the stomach in consort with *slow gastric emptying*,

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i.e., absorption predominantly from the intestinal tract. In effect, lag time can be considered as a *hybrid* parameter.

Despite the obvious significance of lag time as an important parameter in characterizing the absorption kinetics of a drug, most standard biopharmaceutics and pharmacokinetics texts and references have ignored the discussion of lag time completely (17–24). Thus, one might infer, incorrectly, that the inclusion of lag time in pharmacokinetic analyses is unnecessary.

EXPERIMENTAL

Data Collection

To evaluate the effect of lag time, data were obtained from a bioequivalence study and from a series of simulations.

Propoxyphene data for a retrospective analysis (kindly provided by Mylan Pharmaceuticals, Inc.) were obtained from a bioequivalence study involving 24 normal healthy human volunteers. Subjects were administered a single dose of a compressed tablet formulation containing 100 mg of propoxyphene napsylate and 650 mg of acetaminophen. Plasma propoxyphene concentrations were determined at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hr postdose.

Simulated concentration–time data were generated using the equation for a one-compartment open model with lag time:

$$C(t) = \frac{F \cdot D}{V} \frac{K_a}{K_a - K_{el}} [e^{-K_{el}(t-t_{lag})} - e^{-K_a(t-t_{lag})}] \quad (3)$$

where t_{lag} is the lag time. Equation parameter ranges were defined in accordance with tabulations of the pharmacokinetic parameters of drugs (15,25): as most drugs have elimination rate constants in the range of 0.01 to 1.00 hr^{-1} and absorption rate constants in the range of 0.05 to 5.00 hr^{-1}, these ranges were chosen for the simulations. Lag times ranging from 0.05 to 2.00 hr were also chosen for the data simulations. Based on these parameter ranges, 49 data sets with a ratio of K_a to K_{el} in the range of 5 to 15 were simulated. The term FD/V was set equal to 100. Concentration values were then calculated at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, and 24 hr for each set of K_a and K_{el} values.

In a preliminary evaluation of the effect of lag time on a *two*-compartment open model, a few data sets were simulated using the equation for extravascular administration of drug in accordance with a two-compartment open model with first-order microscopic rate constants (1).

Data Analyses

For propoxyphene, individual subject concentration–time data were analyzed by JANA (SCI Software, Lexington, KY), an iterative polyexponential curve-stripping program, to obtain preliminary parameter estimates. Based on these values, PCNONLIN (SCI Software, Lexington, KY) was utilized to refine separately the estimates in agreement with each of the following variations of the one-compartment open model [Eq. (1)]: PCNONLIN model 3, $K_a \neq K_{el}$, no lag time; and PCNONLIN model 4, $K_a \neq K_{el}$, lag time; and

Table I. Pharmacokinetic Parameter Estimates for Propoxyphene Data[a]

Subject	t_{lag}, model 4	K_a		K, model 5	K_{el}	
		Model 3	Model 4		Model 3	Model 4
1	0.93	0.306	1.563	0.302	0.296	0.158
2	0.45	0.361	6.762	0.363	0.365	0.151
3	0.65	0.443	1.527	0.443	0.440	0.254
4	0.19	0.568	0.616	0.575	0.580	0.618
5	a	0.701	a	0.707	0.712	a
6	0.85	0.424	1.279	0.427	0.423	0.428
7	1.06	0.444	2.968	0.454	0.456	0.342
8	0.53	0.925	2.033	0.462	0.242	0.199
9	1.00	0.748	19.778	0.753	0.753	1.307
10	1.77	0.361	5.201	0.362	0.363	0.278
11	0.69	0.376	1.057	0.376	0.376	0.253
12	0.53	0.508	1.939	0.508	0.507	0.296
13	0.69	2.349	7.473	0.657	0.255	0.247
14	0.82	2.123	11.789	0.541	0.127	0.108
15	1.36	0.271	1.326	0.268	0.263	0.215
16	0.53	0.393	0.498	0.392	0.386	0.498
19	a	0.288	a	0.288	0.288	a
20	0.49	0.655	4.132	0.452	0.312	0.181
21	b	0.989	0.698	0.427	0.202	0.227
22	2.73	0.210	2.017	0.209	0.208	0.198
23	0.85	0.439	1.231	0.439	0.438	0.394
24	b	1.591	0.977	0.475	0.196	0.205
25	0.41	0.959	2.932	0.466	0.213	0.158
26	0.70	0.281	0.378	0.281	0.280	0.378

[a] PCNONLIN model 3, one-compartment open model without lag time; PCNONLIN model 4, one-compartment open model with lag time; PCNONLIN model 5, one-compartment open model with equal rate constants and no lag time. (a) No convergence; (b) Lag time <0.

PCNONLIN model 5, $K_a = K_{el}$, no lag time. A convergence criterion of 0.0001 and maximum number of iterations of 50 were set for these analyses. Sum of squares of residuals was minimized using the Newton–Gaussian algorithm.

Simulated concentration–time data, generated using a one-compartment open model with lag time (PCNONLIN model 4), were subsequently analyzed by model 3 of PCNONLIN with no lag time using the same convergence criterion.

Fractional errors in K_a, K_{el}, AUC, C_{max}, and t_{max} were calculated as the ratio of the difference between the expected and the estimated values to the expected value:

$$\text{fractional error} \ldots = \left| \frac{\text{expected value} - \text{estimated value}}{\text{expected value}} \right| \quad (4)$$

The differences in expected and estimated values of parameters were tested for significance by Student's t test at the 95% confidence interval. Based on the weighted sums of squares (WSS) of residuals, certain model selection criteria, i.e., the Akaike information criterion (AIC) (26) and the Schwartz criterion (SC) (27), have been used to test the adequacy of each model. AIC and SC were calculated as follows:

$$\text{AIC} = N_{obs} * \log(\text{WSS}) + 2 * N_{param} \quad (5)$$

$$\text{SC} = N_{obs} * \log(\text{WSS}) + 0.5 * \log(N_{obs}) * N_{param} \quad (6)$$

Table II. Results of Model Selection Criteria from Propoxyphene Data[a]

	AIC		SC	
Subject	Model 3	Model 4	Model 3	Model 4
1	77.56	60.71	75.01	57.32
2	47.36	30.38	44.48	26.53
3	39.83	19.61	36.96	15.76
4	26.94	26.94	23.86	22.82
5	61.43	a	58.55	a
6	91.09	58.94	88.55	55.55
7	59.62	58.94	56.73	55.09
8	28.91	19.82	26.02	15.98
9	54.95	43.25	51.63	38.84
10	51.12	60.25	48.23	56.41
11	65.36	56.81	62.66	53.19
12	60.65	55.38	57.95	51.78
13	8.13	6.93	5.05	2.83
14	2.79	2.17	−0.52	−2.24
15	63.45	43.78	60.75	40.17
16	34.95	28.03	31.87	23.92
19	50.53	a	47.46	a
20	93.42	70.13	91.01	66.93
21	51.55	53.31	48.85	49.71
22	65.63	49.31	62.75	45.47
23	77.29	57.32	74.59	53.72
24	21.27	22.85	18.89	18.74
25	54.43	30.37	51.73	26.76
26	43.37	40.81	40.28	36.69

[a] PCNONLIN model 3, one-compartment open model without lag time; PCNONLIN model 4, one-compartment open model with lag time. (a) Data did not converge to a solution.

Table III. Statistical Analysis of Pharmacokinetic Parameters Computed by PCNONLIN Models 3 and 4

Parameter	Mean diff.	t	df	P
	(A) From propoxyphene data			
K_a	−2.359	−2.738	23	0.012
K_{el}	0.066	1.526	23	0.141
C_{max}	−4.558	−0.719	23	0.480
AUC	51.381	2.109	23	0.046
T_{max}	0.506	3.391	23	0.003
	(B) From simulation data			
K_a	1.623	8.907	48	<0.0001
K_{el}	−0.014	−0.641	48	0.525
C_{max}	17.041	7.471	48	<0.0001
AUC	151.31	1.847	48	0.071
T_{max}	−0.701	−4.735	48	<0.0001

where N_{obs} is the number of observations, WSS is the weighted sum of squares, and N_{param} is the number of parameters estimated in the model.

RESULTS AND DISCUSSION

Propoxyphene Data

One-Compartment Open Model Without Lag Time (PCNONLIN Model 3). The parameter estimates are shown in Table I. These results showed that 17 of 24 subjects have equal absorption and elimination rate constants. This was a totally unexpected outcome. To confirm these findings further, these data were then evaluated by PCNONLIN model 5, a one-compartment open model with equal rate constants and no lag-time.

One-Compartment Open Model with Equal Rate Constants and No Lag Time (PCNONLIN Model 5). Results were in agreement with the results from model 3 for the same 17 of 24 subjects, as shown in Table I, although the magnitude of the rate constants differed substantially among the other 7 subjects. It suggests that these 17 (of 24) subjects appear to have equal rate constants, when data were pharmacokinetically evaluated without a lag time.

One-Compartment Open Model with Lag Time (PCNONLIN Model 4). Results suggest that 19 of 24 subjects have *unequal* rate constants, i.e., $K_a \neq K_{el}$, as shown in Table I. In two subjects, convergence was not achieved within the 50 iteration limit. Subjects 21 and 24 showed a negative lag time, which is an indication that PCNONLIN model 4 is inadequate to describe their data. For these two subjects, from the AIC and SC (Table II), it can be concluded that as the sum of the squared residuals is smaller for PCNONLIN model 3 than for PCNONLIN model 4, model 3 is to be preferred.[4]

[4] Model selection criteria function on the basis of residual sums of squares: If a model attains a solution with a lower WSS than any other model, then it is considered to be better. From Table II, both the AICs and the SCs are lower when PCNONLIN model 4 is used against PCNONLIN model 3, indicating that PCNONLIN model 4 is a better descriptor for the propoxyphene napsylate data.

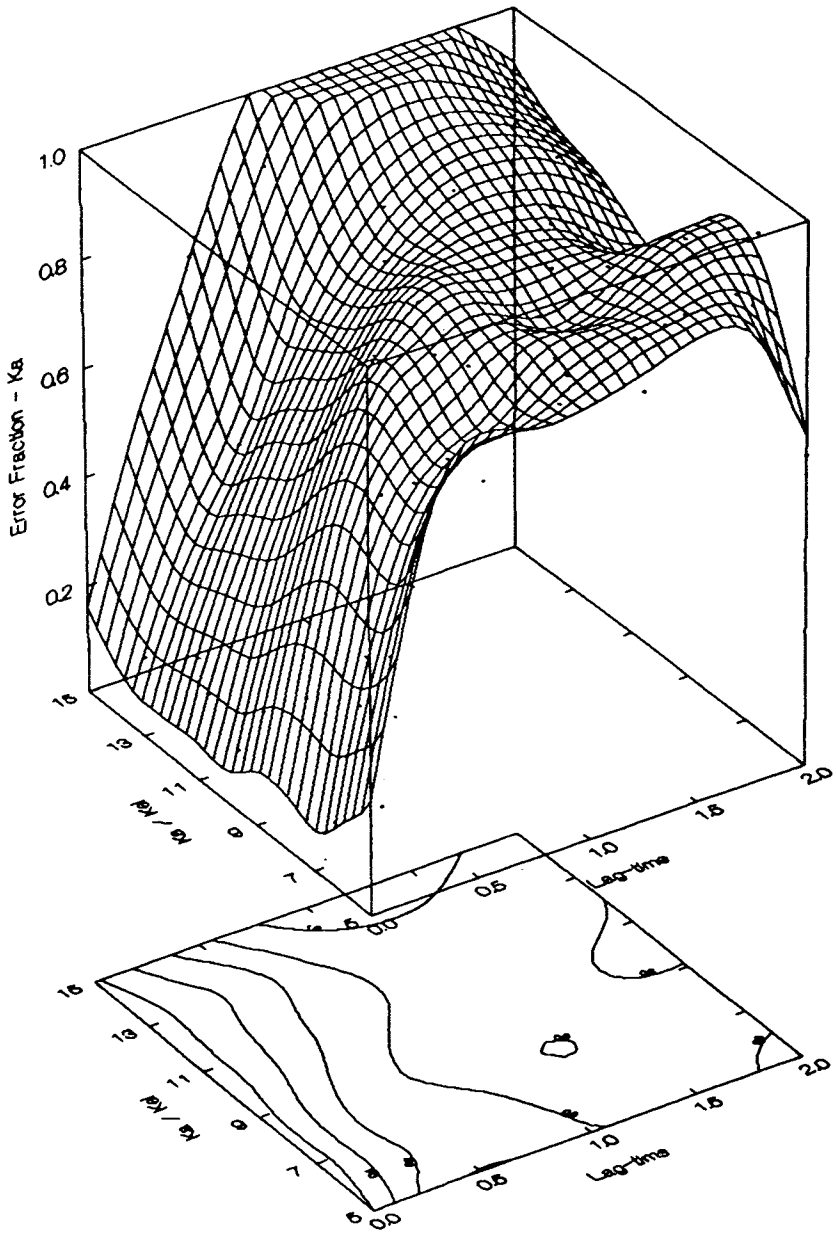

Fig. 1. A response surface representation of the effect of t_{lag} on the error fraction in K_a determined from simulation data analysis.

Statistical Analysis. Student's t test was used to determine if the differences in propoxyphene parameter estimates with the inclusion of a lag time (PCNONLIN models 3 and 4), were significant. The results, provided in Table III, show that lag time had a statistically significant effect on all parameters of a one-compartment open model, except C_{max} and K_{el}, at the 95% confidence level. From Table I, it can also be observed that the lag time ranged from 0.19 to 2.73 hr.

Simulation Data

From the chosen range of elimination rate constants, absorption rate constants, and lag times, 49 data sets were generated based on the equation for PCNONLIN model 4. These 49 data sets were analyzed by PCNONLIN model 3 (one-compartment open model *without* lag time), and 34 of 49 cases resulted in equal rate constants, i.e., $K_a \approx K_{el}$. The differences in parameter estimates, computed with and without the inclusion of lag time in the model, were significant for K_a, C_{max}, and t_{max} (Table III). However, lag time had only a marginal effect on AUC and an insignificant effect on K_{el} at the 95% confidence level (Table III).

Response surfaces (Figs. 1 and 2) were constructed based on these simulation results for K_a and t_{max} using distance-weighted least-squares regression (SYSTAT, Inc., Evanston, IL). These nonplanar response surfaces indicate a nonlinear relationship among (a) the error fraction in parameter estimates of K_a and t_{max}, (b) the ratio of K_a to K_{el}, and (c) lag time: a particular change in lag time does not result in

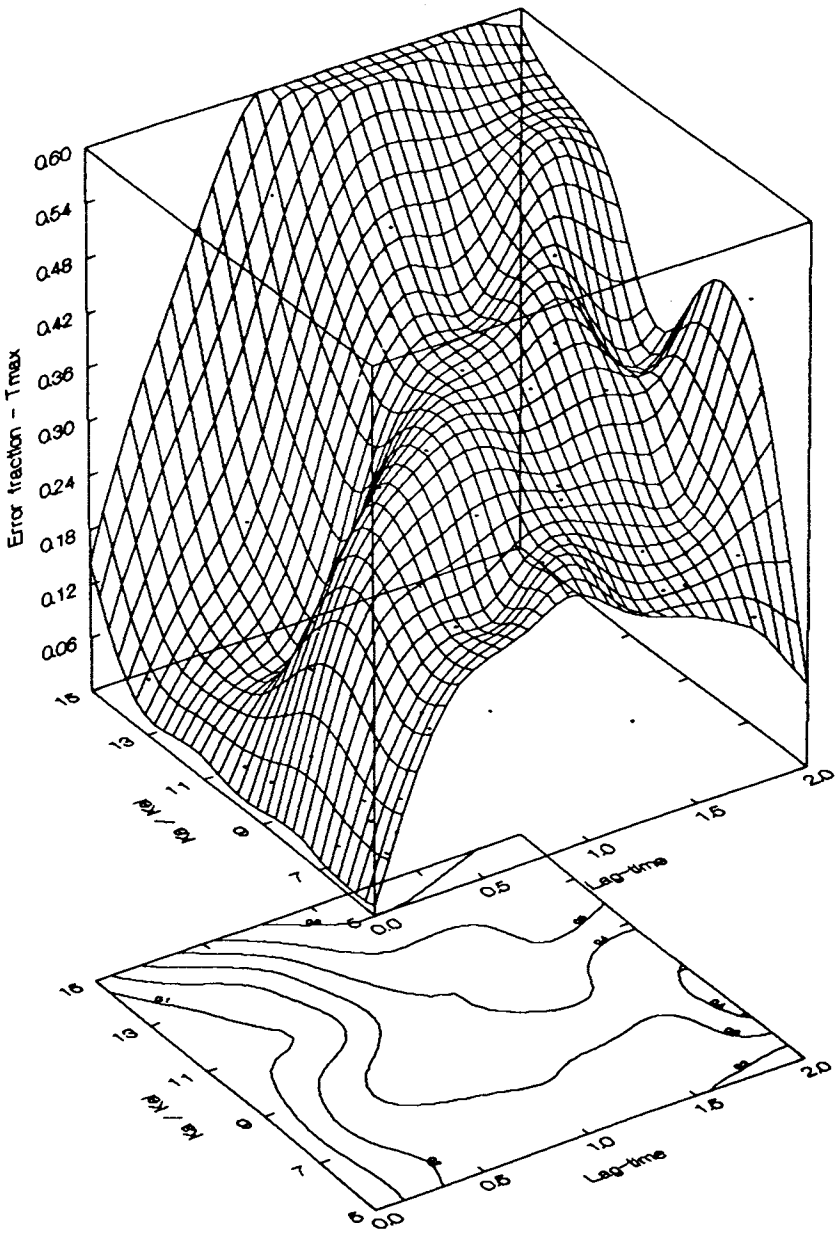

Fig. 2. A response surface representation on the effect of t_{lag} on the error fraction in t_{max} obtained from simulation data analysis.

a corresponding, proportionate change in the error fraction associated with the estimation of K_a. The corresponding contour plots in Figs. 1 and 2 were also generated to delineate further the error fraction boundaries for the parameter estimates. The error fraction boundaries not only clearly establish the substantial impact of large lag times on pharmacokinetic parameter estimation, but also portray the potentially substantial effect of lag times (e.g., 0.10 hr), which ordinarily would be considered to have a negligible effect.

It is evident from both the propoxyphene and the simulation data analyses that lag time has a crucial effect on several parameter estimates. As many secondary parameters (e.g., clearance) are functions of these primary parameters, the error fractions associated with the secondary parameters can multiply enormously, leading to meaningless results.

Preliminary analyses of data obtained from a two-compartment open model suggest that lag time has a significant impact on several pharmacokinetic parameters. This will be the subject of a subsequent report.

CONCLUSIONS

Absence of lag time in a one-compartment open model with first-order absorption and elimination could cause the model to converge to a parameter space with equal rate constants. This observation was confirmed with simulations performed over a wide range of K_{el} (0.01 to 1.00 hr^{-1}) and K_a (0.05 to 5.00 hr^{-1}) values. Lag times as small as 0.10 hr showed a marked effect on several parameters. Lag time showed critical effects on primary and secondary pharma-

cokinetic parameters such as K_a, AUC, and t_{max}. Response surfaces generated from simulation data indicate a nonlinear relationship among the error fraction in parameter estimates of K_a and t_{max}, the ratio of K_a to K_{el}, and lag time.

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