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Estimation of Pharmacokinetic Parameters Using Nonlinear Fixed Effects One Compartment Open Model

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ABSTRACT

Pharmacokinetics (PK) is the science of the kinetics of drug absorption, distribution and elimination. Statistical methods are usually used for PK parameter estimation producing nonlinear responses where drug effect mechanism is modeled using compartmental approach. In the present study, PK parameters were estimated with nonlinear fixed effects one compartment open model where drug dose and sampling time are covariates and the plasma drug concentration is dependent variable. The PK parameters namely absorption rate constant (a), elimination rate constant (b) and apparent volume of distribution (V) were estimated using nonlinear least square method for each individual separately and for all individuals collectively with longitudinal or multiple response plasma drug concentration-time data obtained from 24 healthy human volunteers with reference drug product of Atorvastatin. The estimates for combined data were $\hat{a}$ =0.13±0.13hr^{-1}, $\hat{b}$ =0.49±0.13hr^{-1}, $\hat{V}$ =248±0.05L. All the individuals were again stratified into three categories based on Body Mass Index (BMI) and the PK parameters were estimated for each stratum accordingly (stratum-normal: $\hat{a}$=0.12±0.17hr^{-1}, $\hat{b}$ =0.47±0.17hr^{-1}, $\hat{V}$ =250.24±0.07L; stratum-overweight: $\hat{a}$ =0.15±0.24hr^{-1}, $\hat{b}$ =0.47±0.25hr^{-1}, $\hat{V}$ =267.25±0.09L; stratum-underweight: $\hat{a}$ =0.13±0.13hr^{-1}, $\hat{b}$=0.49±0.13hr^{-1}, $\hat{V}$=245±0.05L).

INTRODUCTION

Pharmacokinetics is the study of kinetics of absorption, distribution, metabolism and excretion (ADME) of drugs and their corresponding pharmacologic, therapeutic, or toxic responses in man and animals (Jambhekar and Breen, 2009). There have been different types of analysis involved to explore the characteristics of pharmacokinetics including parametric and nonparametric (Hauschke et al., 2007). In pharmacokinetic analysis, serial blood samples are collected from each of several subjects following doses of a drug and assayed for drug concentration, and the objective is to characterize pharmacological processes within the body that dictate the time-concentration relationship for individual subjects and the population subjects (Sheiner and Ludden, 1992). A common approach to model the drug concentration over time is to use a compartmental model. Compartmental model is a mathematical representation of the body or an area of the body created to study physiologic or pharmacologic kinetic characteristics. A compartmental model considers the body as made up of a number of compartments through which the drug circulates (Shargel et al., 2010). The nonlinear fixed effects one compartment open model offers the simplest way to describe the process of drug distribution and elimination in the body. This model assumes that the drug can enter or leave the body (i.e., the model is open) and the body acts like a single, uniform compartment (Shargel et al., 2010). A nonlinear regression model with a univariate dependent variable is more frequently used in applications (Gallant, 2008). Nonlinear regression is characterized by the fact that the prediction equation depends nonlinearly on one or more unknown parameters (Smyth, 2002). The nonlinear regression model is a generalization of the linear regression model in which the conditional mean of the response variable is not a linear function of the parameters (Fox and Weisberg, 2011). A popular method for estimating the unknown parameters in a nonlinear regression function is the method of least squares. The nonlinear least squares (nls) method has been used to

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fit a straight line or a flat plane to a bunch of data points especially for plasma drug concentration-time data because the relationship between covariate and response variable is curved (Baker, 2008). The R function nls is used for estimating parameters (Fox and Weisberg, 2011). The self-starting functions are available in R (Pinheiro and Bates, 2000). In the present study an attempt has been taken to estimate the PK parameters namely absorption rate constant (a), elimination rate constant (b) and apparent volume of the distribution (V) using nonlinear fixed effect one compartment open model with longitudinal or multiple response plasma drug concentration-time data.

DATA AND METHODS

The secondary data was collected from Faculty of Pharmacy, University of Dhaka. The trial was conducted to study the pharmacokinetic behavior of Atorvastatin given to 24 randomized non-smoking healthy Bangladeshi male volunteers (Table 1). A 40 mg dose of reference drug product was given to each individual, and following the predetermined protocol blood samples were collected and analyzed to know the concentration at each time point for individual subject. A longitudinal or multiple response data was obtained where plasma drug concentration is the predictable measure (Table 2).

Model Formulation

The nonlinear fixed effects model (Gibaldi and Perrier, 1982) for the j^{th} response on the i^{th} individual can be written as,

$$y_{ijl} = \frac{aD}{V(b-a)}[e^{-at_l} - e^{-bt_l}] + \varepsilon_{ijl} \quad \ldots\ldots\ldots\ldots\ldots (1)$$

Where, a is the absorption rate constant, b is the elimination rate constant, V is the apparent volume of the distribution, D represents the dose, y_{ijl} is the observation taken at time t_l in period j from subject i.

Table 1: Description of the subjects.

Subject	Age	Height (cm)	Weight (kg)
1	23	165.10	60
2	28	162.65	70
3	20	170.05	53
4	24	160.02	65
5	28	167.64	61
6	26	167.64	59
7	29	162.56	53
8	31	160.02	50
9	25	170.18	53
10	27	172.72	65
11	30	160.02	61
12	26	157.48	62
13	28	157.48	61
14	26	162.56	67
15	18	165.10	58
16	20	152.40	64
17	25	170.18	59
18	30	170.18	60
19	31	172.72	64
20	25	157.48	50
21	27	160.02	52
22	35	157.48	58
23	29	160.02	60
24	24	165.10	55

Using nonlinear least square method, the individual specific parameters can be estimated. The actual vector of parameters to be estimated for each individual would be a (3×1) vector, $\beta = (a, b, V)'$

Parameter Estimation Procedure

Least square estimation method was used to estimate the regression parameters a, b and V. The least square approach minimizes the sum of squared errors. The equation (1) can be written as,

$$\varepsilon_{ijl} = y_{ijl} - \frac{aD}{V(b-a)}[e^{-at_l} - e^{-bt_l}]$$

Table 2: Plasma drug concentration (ng/ml) – time (hour) profile for 24 subjects.

Sub.	Time (in hours)						Time (in hours)					
No.	0.5	1	1.5	2	2.5	3	3.5	4	8	12	24	48
1	4.39	10.33	17.46	28.57	35.67	30.22	25.22	21.55	15.47	12.31	5.65	2.39
2	3.59	8.44	13.2	25.74	32.7	40.56	36.07	24.64	15.9	9.32	6.1	3.26
3	6.82	13.77	21.61	29.2	26.19	23.76	19.26	17.48	12.33	11	7.29	2.82
4	3.88	8.58	18.48	31.11	40.87	36.96	30.6	22.12	14.34	9.26	6.99	3.26
5	5.09	9.67	15.15	24.82	36.57	31.72	27.67	22.53	16.42	10	5.37	2.92
6	3.49	5.27	14.9	20.28	27.37	36.79	41.31	30.5	19.85	13.74	4.22	1.58
7	8.8	11.99	15.4	20.61	21.56	25.63	23.34	20.41	16.39	10.23	6.79	2.17
8	7.65	14.78	20.84	32.79	27.11	23.55	20.93	16.24	11.68	9.99	7.66	1.73
9	6.85	12.79	21.68	34.01	31.77	27.65	23.63	20.59	16.84	12.38	5.03	1.9
10	5.03	11.04	16.76	21.43	24.26	27.57	30.51	22.63	15.4	11.37	7.66	2.02
11	6.32	11.07	18.89	30.45	43.87	35.67	30.24	22.76	17.46	10.38	8.26	1.82
12	4.88	8.3	14.77	21.58	30.65	37.18	31.55	25.23	15.01	10.36	6.59	2.49
13	7.04	13.63	20.34	32.33	29.7	27.61	23.12	19.75	14.45	11.35	7.69	2.05
14	5.19	11.48	17.93	21.84	26.74	29.11	26.29	21.39	17.99	12.5	5	1.75
15	6.6	14.16	20.15	25.8	31.26	36.56	30.22	26.48	17.5	10.4	6.35	1.9
16	5.64	11.56	18.22	33.64	30.86	26.05	22.58	20.45	17.24	14.32	4.99	2.64
17	3.36	7.09	10.81	12.23	17.35	21.53	27.85	21.47	16.29	12.2	8.61	2.46
18	7.57	10.5	15.65	18.17	21.33	26.72	30.09	24.56	19.42	13.35	7.57	1.55
19	6.54	14.65	20.02	33.76	45.72	38.69	33.63	27.57	20.45	11.33	6.02	1.92
20	8.04	15.57	22.71	31.69	40.16	36.43	30.58	24.32	19.44	11.31	5.27	1.76
21	5.5	10.67	17.45	21.54	24.17	32.6	37.56	29.47	20.68	13.28	7.04	1.6
22	6.75	14.61	27.24	34.01	29.98	24.51	20.05	17.85	14.34	11.57	6.37	2.01
23	4.36	11.59	14.98	25.28	31.71	39.97	31.6	24.26	17.45	12.26	7.69	1.48
24	6.24	11.8	15.44	18.37	21.63	25.77	30.87	26.21	17.59	12.09	6.85	2.09

Thus, the sum of squared error (SSE) can be expressed as,

$$SSE = \sum_{i=1}^{r} \varepsilon_{ijl}{}^2$$

$$= \sum_{l=1}^{r} [y_{ijl} - \frac{aD}{V(b-a)}[e^{-at_l} - e^{-bt_l}]]^2$$

The minimum of SSE was obtained by setting the derivatives of SSE equal to zero and the estimating equations were as follows-

$$\frac{D}{\hat{V}\sigma^2}\sum_{l=1}^{r}[y_{ijl} - f(t_l;\hat{a},\hat{b},\hat{V})]\left\{\frac{\hat{b}}{(\hat{b}-\hat{a})^2}(e^{-\hat{a}t_l} - e^{-\hat{b}t_l}) - \frac{\hat{a}t_l e^{-\hat{a}t_l}}{(\hat{b}-\hat{a})}\right\} = 0$$

$$\frac{D}{\hat{V}\sigma^2}\sum_{l=1}^{r}[y_{ijl} - f(t_l;\hat{a},\hat{b},\hat{V})]\left\{\frac{\hat{a}t_l e^{-\hat{b}t_l}}{(\hat{b}-\hat{a})} - \frac{\hat{a}}{(\hat{b}-\hat{a})^2}(e^{-\hat{b}t_l} - e^{-\hat{a}t_l})\right\} = 0$$

$$\frac{\hat{a}D}{\hat{V}^2(\hat{b}-\hat{a})}\sum_{l=1}^{r}[y_{ijl} - f(t_l;\hat{a},\hat{b},\hat{V})](e^{-\hat{b}t_l} - e^{-\hat{a}t_l}) = 0$$

To obtain estimates the above equations were need to be solved simultaneously. The Newton-Raphson Iterative procedures can be applied to get the estimates since these equations are not of closed forms for $\hat{a}, \hat{b}$ and $\hat{V}$. The estimates obtained at the m^{th} iteration can be found as,

$\hat{\beta}^{(m)} = \hat{\beta}^{(m-1)} + I^{-1}(\beta)|_{\beta=\hat{\beta}^{(m-1)}} U(\beta)|_{\beta=\hat{\beta}^{(m-1)}}$, m= 1, 2, 3…….

The 'nls' function of R program was used to estimate the pharmacokinetic parameters for each individual separately and all individual collectively. Again all individuals are classified into three strata depending on their BMI and the pharmacokinetic parameters were estimated for each stratum.

RESULTS AND DISCUSSION

The estimated absorption rate constant, elimination rate constant for individual subject were 0.08-0.22 per hour and 0.23-1.01 per hour respectively which are comparable to population pharmacokinetic profile generated with the reference drug product by innovator (Table 3).

Table 3: Parameter estimate of reference drug product for individual subject.

Subject	Estimate		SE	t	p value
1	$\hat{a}$	0.13	0.13	-15.10	0.00
	$\hat{b}$	0.49	0.13	-5.31	0.00
	$\hat{V}$	248	0.05	-38.03	0.00
2	$\hat{a}$	0.10	0.13	-6.21	0.00
	$\hat{b}$	0.48	0.11	0.10	0.01
	$\hat{V}$	252	0.07	-5.5	0.00
3	$\hat{a}$	0.08	0.37	-6.47	0.00
	$\hat{b}$	1.00	0.39	0.12	0.99
	$\hat{V}$	123.8	0.26	-8.12	0.00
4	$\hat{a}$	0.15	1.77	-1.04	0.32
	$\hat{b}$	0.23	1.72	-0.84	0.41
	$\hat{V}$	540.6	0.25	-8.17	0.00
5	$\hat{a}$	0.09	0.55	-4.21	0.00
	$\hat{b}$	0.70	0.56	-0.61	0.55
	$\hat{V}$	179	0.33	-6.26	0.00
6	$\hat{a}$	0.13	0.71	-2.80	0.01
	$\hat{b}$	0.37	0.69	-1.40	0.19
	$\hat{V}$	309.8	0.24	-8.93	0.00
7	$\hat{a}$	0.08	0.23	-10.57	0.00
	$\hat{b}$	0.65	0.23	-1.86	0.09
	$\hat{V}$	175.9	0.13	-15.76	0.00
8	$\hat{a}$	0.10	0.43	-5.07	0.00
	$\hat{b}$	0.98	0.45	-0.025	0.98
	$\hat{V}$	142.8	0.28	0.28	0.00
9	$\hat{a}$	0.11	0.42	-5.14	0.00
	$\hat{b}$	0.73	0.44	-0.69	0.50
	$\hat{V}$	160.6	0.24	-8.59	0.00
10	$\hat{a}$	0.11	0.44	-4.86	0.00
	$\hat{b}$	0.48	0.43	-1.65	0.12
	$\hat{V}$	244.0	0.19	-10.73	0.00
11	$\hat{a}$,	0.19	1.21	-1.32	0.21
	$\hat{b}$	0.41	1.24	-0.71	0.49
	$\hat{V}$	312.7	0.29	-6.85	0.00
12	$\hat{a}$	0.13	0.62	-3.21	0.00
	$\hat{b}$	0.72	0.64	-0.48	0.63
	$\hat{V}$	193.2	0.33	-5.81	0.00
13	$\hat{a}$	0.09	0.44	-5.34	0.00
	$\hat{b}$	0.65	0.44	-0.92	0.37
	$\hat{V}$	162.0	0.26	-8.57	0.00
14	$\hat{a}$	0.11	0.35	-6.06	0.00
	$\hat{b}$	0.48	0.35	-2.06	0.06
	$\hat{V}$	241.3	0.15	-13.49	0.00
15	$\hat{a}$	0.11	0.35	-6.06	0.00
	$\hat{b}$	0.48	0.35	-2.06	0.06
	$\hat{V}$	241.3	0.15	-13.49	0.00
16	$\hat{a}$	0.09	0.47	-5.01	0.00
	$\hat{b}$	0.70	0.48	-0.71	0.48
	$\hat{V}$	151.1	0.28	-7.83	0.00
17	$\hat{a}$	0.09	0.33	-6.85	0.00
	$\hat{b}$	0.39	0.32	-2.59	0.02
	$\hat{V}$	247.1	0.15	-14.52	0.00
18	$\hat{a}$	0.09	0.33	-6.85	0.00
	$\hat{b}$	0.43	0.32	-2.59	0.02
	$\hat{V}$	231.2	0.15	-14.52	0.00
19	$\hat{a}$	0.11	0.53	-4.02	0.00
	$\hat{b}$	0.69	0.55	-0.67	0.51
	$\hat{V}$	177.8	0.29	-7.07	0.00
20	$\hat{a}$	0.16	0.54	-3.30	0.00
	$\hat{b}$	0.51	0.56	-1.18	0.26
	$\hat{V}$	233.3	0.20	-10.35	0.00
21	$\hat{a}$	0.22	2.05	2.05	-0.72
	$\hat{b}$	0.33	2.06	2.06	-0.53
	$\hat{V}$	412.7	0.26	0.26	-7.50
22	$\hat{a}$	0.10	0.44	-5.11	0.00
	$\hat{b}$	1.01	0.46	0.02	0.98
	$\hat{V}$	125.8	0.29	-7.06	0.00
23	$\hat{a}$	0.18	1.27	-1.33	0.21
	$\hat{b}$	0.34	1.26	-0.83	0.42
	$\hat{V}$	345.7	0.27	-7.74	0.00
24	$\hat{a}$	0.12	0.44	-4.76	0.00
	$\hat{b}$	0.39	0.42	-2.16	0.05
	$\hat{V}$	287.5	0.16	-12.94	0.00

The volume of distribution for all individual was ranged between 123.8 L and 540.6 L which conforms to the physicochemical properties of Atorvastatin assuring suitability of the proposed method. It was observed that the estimated absorption rate constant, elimination rate constant and volume of distribution were 0.13±0.13 per hour, 0.49±0.13 per hour and 248±0.05 L with 95% level of significance respectively for all individual subjects collectively (Table 4).

Table 4: Parameter estimates of reference drug product for all subjects collectively.

	Estimate	SE	t	p value
$\hat{a}$	0.13	0.13	-15.10	0.00
$\hat{b}$	0.49	0.13	-5.31	0.00
$\hat{V}$	248	0.05	-38.03	0.00

The parameters were estimated with minimum variability indicating robustness of the proposed method. There were no significance variations in the absorption and elimination rate constants but a significant difference in volume of distribution was obtained in three strata (Underweight: 245 L; Normal: 250.24 L; Overweight: 267.25 L) which infers that the model was successful to ascertain the distribution pattern of drug in various patients depending on their BMI (Table 5).

Table 5: Parameter estimates of reference drug product for different stratum.

Stratum		Estimate	SE	t	p value
Normal	$\hat{a}$	0.12	0.17	-11.97	0.00
	$\hat{b}$	0.47	0.17	-4.33	0.00
	$\hat{V}$	250.24	0.07	-29.51	0.00
Overweight	$\hat{a}$	0.15	0.24	-7.73	0.00
	$\hat{b}$	0.47	0.25	-2.97	0.00
	$\hat{V}$	267.25	0.09	-22.71	0.00
Underweight	$\hat{a}$	0.13	0.13	-13.55	0.00
	$\hat{b}$	0.49	0.13	-5.56	0.00
	$\hat{V}$	245	0.05	-21.89	0.00

A lipophilic drug like Atorvastatin will be preferentially distributed into adipose tissue thereby decreasing plasma drug concentration resulting in higher value of apparent volume of distribution. The adipose tissue mass is higher in case of obese patient than that of normal and underweight resulting in more drug partitioning and the highest value of volume of distribution.

CONCLUSION

The developed method can be utilized for pharmacokinetic parameter estimation in various biopharmaceutical studies. The method developed is simple, efficient and accurate, and will open a door for researcher as well as drug product manufacturers to know the pharmacokinetic parameters from any plasma drug concentration- time profile for bioequivalence studies.

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