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Pharmacokinetic Modelling of Lamotrigine from Plasma Concentrations in Healthy Volunteers

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Abstract

The pharmacokinetics of the antiepileptic agent lamotrigine (CAS 84057-84-1) was investigated after single oral doses in 14 healthy volunteers. After the administration of single oral doses of 2x100 mg lamotrigine chewable/soluble tablets to healthy volunteers, blood samples were collected for the next 96 h. The pharmacokinetic modelling of lamotrigine showed that the drug exhibited two compartment open model with regard to the goodness of fits, Residual Sum of Squares (RSS), Akaike's Information Criteria (AIC), Schwartz Criteria (SC), standard deviation of the regression (Sr), and determination coefficient (r^2). The time-concentration curves showed a mean time to reach peak plasma concentration, C_{max} (t_{max}) of 2.0 h. The pharmacokinetic parameters were calculated based on the plasma curves. Area under the curve of concentration versus time from zero to infinity ($AUC_{0\to\infty}$), systemic clearance (Cl), apparent volume of distribution (V_{darea}), apparent volume of distribution at steady state (V_{dss}), apparent volume of distribution for I.V. (V_{dext}), and mean residence time (MRT) were found to be 128±31 µg.h/mL, 1.63±0.39 L/h, 88.5±28.6 L, 83.2±23.6 L, 93.2±35.6 L, and 62.6±13.7 h (mean±SD), respectively. Compartmental analysis demonstrated that oral lamotrigine tablets obey two compartment open model with rapid absorption and a relatively long half life.

Keywords: Lamotrigine; Pharmacokinetics; Modelling

Introduction

Being a member of the phenyltriazine class, lamotrigine (6-(2, 3-dichlorophenyl)-1, 2, 4-triazine-3, 5-diamine, CAS 84057-84-1) is an anticonvulsant, that has a novel chemical structure and mechanism of action (Goa et al., 1993). It exerts its antiepileptic effects by blocking the voltage-sensitive sodium channels and inhibiting the release of glutamate (LaRoche, 2007; Stefan et al., 2007). Lamotrigine exhibits a broad spectrum of efficacy, being active against partial seizures with or without secondary generalization, primarily generalized tonic-clonic seizures, absence seizures, and drop attacks associated with the Lennox-Gastaut Syndrome (Perucca, 1996; Frank et al., 1999; Motte et al., 1997). The present study is designed to carry out the pharmacokinetic modelling of lamotrigine in plasma after the administration of a single oral dose to 14 healthy volunteers.

Materials and Methods

Clinical protocol

The study was an open-label, single period, single-dose study. 14 healthy volunteers, nine males and five females within 10 % of their ideal body weight participated in the study. Their mean age was 23±2 years. After the administration of single oral doses of 2x100 mg lamotrigine chewable/soluble tablets (LAMICTAL™ DC 100mg chewable/soluble tablets, GlaxoWellcome, Istanbul, Turkey, batch no. B117131) to volunteers, blood samples were collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, 72 and 96 h. Study design and drug analysis details can be found in the previous paper by the authors (Incecayir et al., 2007).

Data analysis

Most of the plasma concentration data were modelled by the program KINETICA™(Version 3.1; Philadelphia, USA). Some of the data were stripped with the programme ESTRIP (Brown et al., 1978), while two were fit manually (Wagner, 1979). Both ESTRIP and manual fits were further optimized by nonlinear regression, using the program SPSS v.11.5.

The mean time to reach peak plasma concentration, $C_{max,}$ (t_{max}) for a three exponential function cannot be determined directly, as for a two exponential model. Iterative techniques as described by Wagner, (1979) has been employed for this purpose for each subject equation. C_{max}'s have then been calculated by substitution in the respective equations.

Results

The semilogarithmic mean plasma concentration-time profile of lamotrigine during 96 h. in 14 healthy volunteers are shown in Figure 1.

The data were fit both to one compartment and two compartment open models. The equations describing the compartments are as follows:

$$C_p = C_1 e^{-k_d t} + C_2 e^{-k_a t} \quad \text{One comp. model}$$

$$C_p = C_1 e^{-\alpha t} + C_2 e^{-\beta t} + C_3 e^{-k_a t} \quad \text{Two comp. model}$$

where, C_p is the plasma concentration (µg/mL); k_d, β, disposition rate constants(h^{-1}); k_a, absorption rate constant(h^{-1}); α, distribution rate constant(h^{-1}); and C_i's, coefficients(µg/mL). α, β, C_1, C_2 and C_3 are the macrorate constants. Obtained macro pa-

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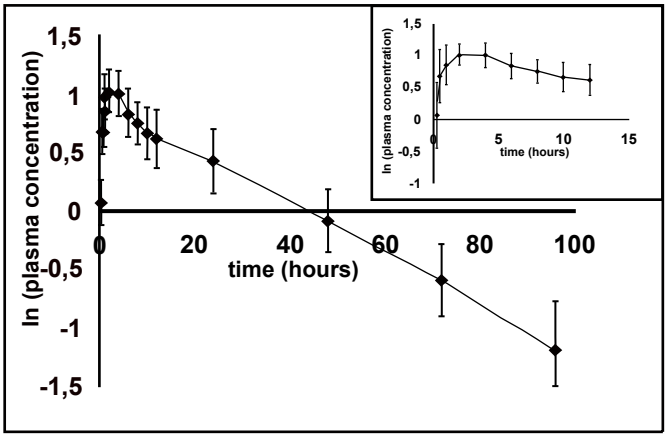

Figure 1: Semilogarithmic mean plasma concentration-time profiles of lamotrigine in 14 healthy volunteers(with standard deviations).

SUBJECT	C_1 (µg/mL)[a]	C_2 (µg/mL)[b]	k_d (h^{-1})[c]	K_a (h^{-1})[d]
1	2.95	-2.95	0.0196	2.28
2	2.39	-2.39	0.0244	2.54
3	3.78	-3.78	0.0268	2.11
4	2.58	-2.58	0.0230	1.24
5	2.71	-2.71	0.0295	3.54
6	2.53	-2.53	0.0664	2.14
7	3.75	-3.75	0.0328	4.51
8	2.76	-2.76	0.0178	3.00
9	2.60	-2.60	0.0188	0.694
10	2.54	-2.54	0.0190	3.83
11	2.80	-2.80	0.0260	1.58
12	3.41	-3.41	0.0231	2.54
13	2.62	-2.62	0.0298	5.13
14	2.75	-2.75	0.0343	5.06
Mean	2.87	-2.87	0.0279	2.87
SD[e]	0.45	0.45	0.0123	1.38
CV%[f]	15.7	-15.7	43.9	48.0

[a, b]macrorate constants; [c]disposition rate constants (h^{-1}); [d]absorption rate const. (h^{-1}); [e]Standard deviation; [f]Coefficient of variation.

Table 1: One compartment macroparameters.

rameters for one and two compartment models are depicted in Tables 1 and 2.

Goodness of fits were assessed with Residual Sum of Squares (RSS), Akaike's Information Criteria (AIC), Schwartz Criteria (SC), standard deviation of the regression (Sr) and determination coefficient (r^2). Fits for one and two compartment models are given in Tables 3 and 4.

Microrate constants calculated from two compartment model are given in Table 5 and other pharmacokinetic parameters in Table 6.

Discussion

In pharmacokinetic data analysis, it is necessary to select the correct model, allowing estimation of pharmacokinetic parameters with small bias and good precision, and to select a model, allowing precise predictions of concentrations. Therefore, the present study was designed to carry out plasma pharmacokinetics of lamotrigine in 14 healthy volunteers after the administration of single oral doses of 200 mg. In our previous paper (Incecayir et al., 2007), only noncompartmental approach was employed to data, whereas full pharmacokinetic modelling is employed in this paper. It was seen that two compartment fits gave better results than one compartment fits with regard to all five criteria, RSS, AIC, SC, Sr and r^2 (Figure 2). From Figure 1, which is a semilogarithmic plot, the two phase disposition is also apparent.

While some investigators (Yuen et al., 1987) declared that lamotrigine pharmacokinetics can be described by the one-compartment open model, the detailed statistical analysis conducted in this study with 14 volunteers' single dose data demonstrated that two compartmental open model was the correct pharmacokinetic model for lamotrigine. It is certainly known that lamotrigine is widely distributed to all organs and tissues, including brain tissue (Ramsay et al., 1991). In a study, a mean brain:serum ratio of 2.8 was found in 11 patients with brain tumors who had received lamotrigine 100-400 mg/day from one day to 17 months (Goldsmith et al., 2003). Such a good distribution of lamotrigine in the brain is certainly a result of the basic and lipophilic properties of the molecule, which permits it to cross the blood-brain barrier easily and have high affinity to the brain tissue (Castel-Branco et al., 2003). Also, a study (Garnett, 1997) assessed the ability of lamotrigine and its glucuronide metabolite to penetrate the blood-brain barrier in a 10-year-old epileptic patient, who underwent a frontal topectomy to remove seizure-causing foci in the cerebral cortex, approximately four

SUBJECT	C_1 (µg/mL)[a]	C_2 (µg/mL)[b]	C_3 (µg/mL)[c]	β (h^{-1})[d]	α (h^{-1})[e]	k_a (h^{-1})[f]
1	2.06	49.2	-51.3	0.0108	0.507	0.569
2	2.30	9.85	-12.2	0.0229	1.27	1.48
3	2.91	0.952	-3.86	0.0225	0.0557	2.03
4	2.13	28.9	-31.0	0.0176	0.481	0.534
5	2.00	1.69	-3.68	0.0182	0.280	2.36
6	1.02	2.75	-3.77	0.0135	0.243	1.32
7	2.97	1.30	-4.27	0.0239	0.194	3.45
8	2.62	15.0	-17.6	0.0161	1.32	1.55
9	3.87	-1.36	-12.51	0.0231	0.0398	0.726
10	2.24	0.476	-2.71	0.0162	0.122	3.27
11	2.60	22.1	-24.7	0.0233	0.722	0.801
12	3.04	1.14	-4.18	0.0195	0.283	1.90
13	1.87	1.01	-2.88	0.0198	0.123	4.12
14	1.46	1.42	-2.89	0.0205	0.0707	4.41
Mean	2.36	9.60	-12.0	0.0191	0.408	2.04
SD[g]	0.72	14.67	-14.6	0.0040	0.423	1.31
CV%[h]	30.3	153	122	20.8	104	64.3

[a, b, c]macrorate constants; [d]disposition rate constants (h^{-1}); [e]absorption rate const. (h^{-1}); [f]absorption rate const.(h^{-1}); [g]Standard deviation; [h]Coefficient of variation.

Table 2: Two compartment macroparameters.

SUBJECT	RSS[a]	AIC[b]	SC[c]	S_r[d]	r^2[e]
1	2.12	18.5	22.1	0.460	0.835
2	0.375	-5.73	-3.17	0.194	0.956
3	0.236	12.2	-9.66	0.154	0.988
4	0.450	-3.19	-0.636	0.212	0.950
5	1.90	17.0	19.5	0.436	0.849
6	0.656	2.11	4.66	0.256	0.906
7	0.662	2.23	4.79	0.257	0.970
8	0.757	4.10	6.65	0.275	0.931
9	0.144	-19.1	-16.6	0.120	0.984
10	0.221	-13.1	-10.6	0.149	0.975
11	0.153	-18.3	-15.7	0.124	0.986
12	0.603	0.918	3.47	0.246	0.964
13	0.233	-12.4	-9.82	0.153	0.978
14	0.315	-8.17	-5.61	0.178	0.974
Mean	0.630	-3.38	-0.828	0.229	0.946
SD[f]	0.620	11.71	11.71	0.106	0.050

[a]Residual sum of squares; [b]Akaike's Information Criteria; [c]Schwartz Criterion; [d]Standard deviation of the regression; [e]Determination Coefficient; [f]Standard deviation.

Table 3: One compartment fits.

SUBJECT	RSS[a]	AIC[b]	SC[c]	S_r[d]	r^2[e]
1	0.601	4.87	8.70	0.274	0.953
2	0.333	-3.39	0.449	0.204	0.961
3	0.225	-8.90	-5.06	0.168	0.989
4	0.178	-12.2	-8.33	0.149	0.980
5	1.31	15.8	19.6	0.405	0.896
6	0.0431	-32.0	-28.2	0.0734	0.994
7	0.369	-1.97	1.86	0.215	0.983
8	0.589	4.58	8.41	0.271	0.946
9	0.138	-15.7	-11.9	0.132	0.984
10	0.186	-11.6	-7.74	0.152	0.979
11	0.0594	-27.5	-23.7	0.0861	0.995
12	0.427	0.0841	3.92	0.231	0.974
13	0.101	-20.1	-16.3	0.112	0.990
14	0.263	-6.71	-2.87	0.181	0.978
Mean	0.344	-8.20	-4.36	0.190	0.972
SD[f]	0.329	13.03	13.03	0.088	0.026

[a]Residual sum of squares; [b]Akaike's Information Criteria; [c]Schwartz Criteria; [d]Standard deviation of the regression; [e]Determination Coefficient; [f]Standard deviation.

Table 4: Two compartment fits.

SUBJECT	V_p/FF*[a] (L)	k_{12}[b] (h^{-1})	K_{el}[c] (h^{-1})	K_{21}[d] (h^{-1})
1	26.4	0.334	0.0375	0.146
2	53.1	0.466	0.0368	0.786
3	51.6	0.00428	0.0263	0.0476
4	39.4	0.248	0.0404	0.210
5	56.5	0.100	0.0304	0.167
6	60.2	0.133	0.0388	0.0846
7	46.9	0.0418	0.0322	0.144
8	41.1	0.585	0.0294	0.725
9	79.7	-0.00457	0.0190	0.0485
10	73.1	0.0153	0.0190	0.140
11	41.5	0.307	0.0424	0.395
12	49.3	0.0586	0.0252	0.219
13	69.0	0.0275	0.0279	0.0878
14	68.6	0.0137	0.0314	0.0461
Mean	54.0	0.166	0.0312	0.229
SD[e]	14.9	0.191	0.0074	0.241
CV%[f]	27.6	115	23.8	105

[a]Apparent distribution volume with bioavailability coefficient; [b]Rate constant from the central to the peripheral compartment; [c]Rate constant for elimination from the central compartment; [d]Rate constant from the peripheral to central compartment; [e]Standard deviation; [f]Coefficient of variation.

Table 5: Microrate constants for the two compartment open model.

SUBJECT	$t_{½}$[a] (h)	MRT[b] (h)	t_{max}[c] (h)	C_{max}[d] (µg./mL)	AUC[e] (µg.h/mL)	Cl[f] (L/h)	V_{darea}[g] (L)	V_{dss}[h] (L)	V_{dex}[i] (L)
1	64.3	96.5	2.47	3.51	198	1.01	92.9	87.0	97.1
2	30.3	45.2	1.58	2.38	100	1.97	86.3	84.5	86.4
3	30.8	62.9	2.10	3.57	144	1.37	60.9	56.2	68.2
4	39.3	60.7	3.09	2.62	123	1.61	91.3	86.0	95.0
5	38.1	59.0	1.35	2.95	114	1.73	95.3	90.3	99.0
6	51.2	78.7	1.86	2.42	83.8	2.36	174	155	194
7	29.0	47.2	1.16	3.85	130	1.53	63.9	60.5	66.5
8	43.1	63.5	1.35	2.90	163	1.22	75.6	74.2	75.7
9	30.0	69.7	5.43	2.27	130	1.53	66.0	72.2	52.3
10	42.8	70.2	1.42	2.56	141	1.40	86.6	83.8	88.1
11	29.8	45.6	2.44	2.76	111	1.78	76.4	73.7	77.8
12	35.6	55.4	1.82	3.48	158	1.26	64.4	62.5	65.2
13	34.9	58.8	1.07	2.68	102	1.94	98.0	90.7	105
14	33.9	63.2	1.05	2.72	90.9	2.18	106	89.0	135
Mean	38.1	62.6	2.01	2.91	128	1.63	88.5	83.2	93.2
SD[j]	9.9	13.7	1.15	0.50	31	0.39	28.6	23.6	35.6
CV%[k]	26.0	21.8	57.3	17.2	24.4	23.6	32.4	28.4	38.2

[a]Biological half-life; [b]Mean Residence Time; [c]Estimated time to reach maximum plasma concentration; [d]Estimated maximum plasma concentration; [e]Area under the curve to infinity; [f]Systemic clearance; [g]Apparent volume of distribution from area; [h]Apparent volume of distribution at steady state; [i]Apparent volume of distribution for I.V.; [j]Standard deviation; [k]Coefficient of variation.

Table 6: Other pharmacokinetic parameters flor the two compartment open model.

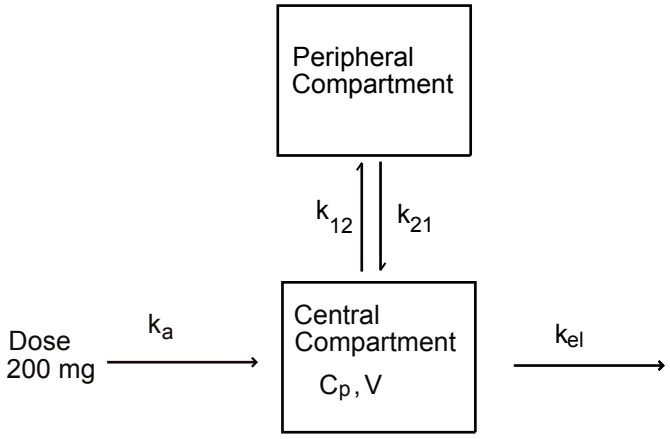

Figure 2: The two compartmental open model of lamotrigine in healthy volunteers (C_p: Plasma concentration (µg/mL), V: Apparent distribution volume(L), k_a: Absorption rate const.(h^{-1}), k_{el}: Rate constant for elimination from the central compartment(h^{-1}), k_{12}: Rate constant from the central to the peripheral compartment(h^{-1}), k_{21}: Rate constant from the peripheral to central compartment(h^{-1})).

hours after the last dose. The concentration of lamotrigine in the brain was higher than the unbound concentration in plasma. On the other hand, concentrations of lamotrigine glucuronide were very low in the brain. On the basis of this result, the good transport of lamotrigine to the brain might explain the data obeying two compartment open model in the present study. Moreover, brain seems to play a role as a peripheral compartment in the two-comparment open model of lamotrigine, which is needed to be proven in future researches.

Previous investigations (Btaiche et al., 1995; Perucca, 1999) in healthy individuals demonstrated that lamotrigine is rapidly absorbed from the gastrointestinal tract. After an oral dose C_{max} occurs within 1 to 3 hours. This study also showed that absorption of lamotrigine appeared rapid with a t_{max} of 2.0 h.

The biological half-life ($t_{½}$) of lamotrigine was approximately 38 h, which is longer than those reported as 24.1 to 31.2 h following single oral doses in healthy adults by other researchers (Yuen et al., 1987; Cohen et al., 1987; Goa et al., 1993). Mean residence time (MRT) of lamotrigine after oral administration, was 62.6 ± 13.7 h. It was shown that long $t_{½}$ and MRT allows once or twice-daily administration of lamotrigine, which has been already used in this dosage regimen in clinical situations. Yau et al., (1991) indicated the dose proportionality of lamotrigine at single oral doses of 50, 200, 400 mg in 20 subjects. The area under the curve of concentration versus time (AUC) for 200 mg dose was 109.4±36.6 µg.h/mL, which is very close to the AUC value of 128±31 µg.h /mL found in the present study.

Systemic clearance (Cl) of 1.63±0.39 L/h and apparent volume of distribution (V_{darea}) of 88.5±28.6 L found in this study are comparable to the others reported by most investigators (Yuen et al., 1987; Cohen et al., 1987; Goa et al., 1993; Elwes et al., 1996). No lag time was demonstrated in this study. As a result, it is known that lamotrigine is well absorbed; there is negligible first pass effect and bioavailability is virtually 100 % (Yuen et al., 1987; Gram, 1996).

Researchers have conducted several investigations on the pharmacokinetics of single and multiple doses of lamotrigine, influence of age, comedication, and disease state on lamotrigine pharmacokinetics in both healthy individuals and patients. However, the present study conducted in healthy volunteers receiving single oral dose of lamotrigine, approaches to the pharmacokinetics of lamotrigine in a different perspective of mathematical modelling.

Overall, on the basis of the detailed compartmental analysis, the results of this single dose study demonstrated that oral lamotrigine tablets obey two compartment open model with rapid absorption and a relatively long half life.

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