

Therapeutic Window of Lamotrigine for Mood Disorders: A Naturalistic Retrospective Study

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Abstract

Introduction: Lamotrigine is widely used for mood disorders including bipolar disorder and major depression, but its therapeutic levels have yet to be determined. This study was conducted to investigate the hypothesis that lamotrigine may have a therapeutic window for mood disorders.

Methods: 25 patients with mood disorders received lamotrigine for more than one year during which time plasma lamotrigine levels were measured at least once. Their mental state was retrospectively and regularly but blindly assessed using the Clinical Global Impression–Severity (CGI-S) scale. In order to investigate our hypothesis, we depicted the relationship between the last lamotrigine levels and the last CGI scores in

25 patients. If any, the potential therapeutic window was further investigated.

Results: The relationship between the last lamotrigine levels and the last CGI scores in the 25 patients indicated the presence of a therapeutic window of lamotrigine from 5 to 11 µg/mL. The repeated measures of ANOVA reached a significant tendency of the effects of lamotrigine levels within 5–11 µg/mL on better CGI-S scores, and the CGI-S scores at the last observation of the 15 patients whose lamotrigine levels were within 5–11 µg/mL were significantly better than those of 10 patients whose lamotrigine levels were not within 5–11 µg/mL.

Conclusion: These findings suggest that lamotrigine may have a therapeutic window for patients with mood disorder from 5 to 11 µg/mL.

Introduction

Lamotrigine has a modest but significant antidepressant effect [1–4] and a prophylactic effect particularly for depressive relapse in bipolar disorders [5–7]. The number needed to treat for prevention of any mood episode was calculated as 5–11 [8]. However, given the negative trial of manic state and the length of time for titration up to a therapeutic dose, lamotrigine is not indicated for the acute treatment of mania [9]. Therefore, lamotrigine has a different therapeutic profile compared to other mood stabilizers such as lithium, valproate and carbamazepine.

Although therapeutic drug monitoring (TDM) of lamotrigine for epilepsy is recommended and the therapeutic levels are reported to be 3–14 µg/mL [10], so far, no specific reference range has been reported for mood stabilizing effects of lamotrigine [10]. In the present study, we hypothesized that lamotrigine may have a therapeutic window for mood disorders.

Patients and Methods

This is a naturalistic and retrospective study. In April 2013, we identified 25 patients who suffered from mood disorders, received lamotrigine for more than one year, and measured plasma lamotrigine levels at least once. First, their mental state was retrospectively and as regularly as possible assessed at 1 month before, just before, 1, 3, 6, 12 months after starting lamotrigine, and thereafter at 18, 24, 30, 36, 42, and 48 months until its discontinuation. The assessment was performed using each patient's clinical records close to the above scheduled months by a blinded researcher (i.e., Y.K. showed the anonymous clinical records without stating the dates to T.T. who assessed the mental state independently and blindly) using Clinical Global Impression – Severity scale (1 = normal, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = the most extremely ill [11]). Secondly, Y.K. identified the last lamotrigine

levels on or close to the date when the last clinical records were described for the aforementioned retrospective CGI-S assessment. If the day of measuring lamotrigine and the date when the clinical records for the CGI-S assessment were described were different, the difference was permitted if lamotrigine dose was unchanged between the day of measuring lamotrigine and the date when the clinical records for the CGI-S assessment were described. CGI-S scores were blind to lamotrigine TDM (by Y.K.) and CGI-S ratings (by T.T.) and were never influenced by lamotrigine TDM.

Subjects

As shown in **Table 1**, subjects were 25 patients (15 males and 10 females), aged between 26 and 69 years (mean=44.9, SD=12.9). 18 patients had bipolar II disorder (BP II), 2 had bipolar I disorder (BP I) and 5 had major depressive disorder (MD). Their CGI-S scores at 1 month before and just before starting lamotrigine ranged from 2 to 5 (mean=3.5, SD=0.8) and 3–5 (mean=4.2, SD=0.7), respectively. Just before starting lamotrigine, 18 patients had mood stabilizers other than lamotrigine, 15 patients had antidepressants, and 6 patients had antipsychotics. Lamotrigine was started in combination with these drugs. The starting dose of lamotrigine ranged from 12.5 to 50 mg/day (mean=19.5, SD=8.9), which was gradually increased to 50–400 mg/day (mean=256.0, SD=99.0) at the last observation.

Measurement of plasma lamotrigine levels

All the blood samples for measurement of plasma lamotrigine levels were taken approximately 12 h after the last dose of lamotrigine. All lamotrigine doses were unchanged for more than the

6 days which are required to obtain lamotrigine levels in a steady state. Valproate was combined with lamotrigine in 7 patients while carbamazepine was combined with lamotrigine in 2 patients, but their doses were unchanged for more than 2 months and their effects on lamotrigine levels also seemed to be in a steady state. The measurement of lamotrigine was performed using a HPLC system by a third party. The inter- and intra-assay coefficients of variation were 2.79 and 0.58%, respectively.

Statistical analyses

In order to investigate our hypothesis that lamotrigine may have a therapeutic window for mood disorders, we depicted the relationship between the last lamotrigine level and the last CGI score in 25 patients. If any, using the potential therapeutic window, repeated measures of analysis of variance (ANOVA) were performed using the CGI-S scores at baseline (i.e., just before starting lamotrigine) and the last CGI-S scores as a dependent factor with the last lamotrigine levels (within the potential therapeutic window or not) as an independent factor. Secondly, the last CGI-S scores were compared between patients whose lamotrigine levels were within the potential therapeutic window and patients whose lamotrigine levels were not within the window by unpaired t-test.

Ethics

The study was approved by the ethics committee of Oita University Faculty of Medicine. All subjects gave written informed consent.

Table 1 Patient demographics and lamotrigine levels and CGI-S scores.

Patient #	Gender	Age	Dx	Lamotrigine levels (µg/mL) at the last observation	Within 5–11 µg/mL or not	Lamotrigine administration period until the last observation (months)	CGI-S at baseline	CGI-S at the last observation
1	m	46	MD	7.21	y	12	5	2
2	m	38	BP II	4.24	n	18	5	3
3	m	62	MD	5.18	y	18	5	1
4	m	35	BP II	11.28	n	36	5	2
5	f	39	BP II	11.86	n	24	5	3
6	f	36	BP II	6.05	y	6	4	2
7	f	38	BP II	9.31	y	24	4	3
8	m	52	BP II	7.29	y	18	3	2
9	m	26	BP II	10.36	y	18	4	2
10	m	52	BP II	10.83	y	24	4	2
11	m	46	BP II	8.84	y	48	5	2
12	f	28	MD	14.13	n	12	4	4
13	f	60	BP II	5.85	y	48	5	3
14	m	35	BP II	3.83	n	18	4	2
15	m	38	BP II	4.26	n	42	4	4
16	f	69	BP I	6.89	y	36	3	2
17	m	61	BP II	2.22	n	12	3	2
18	f	63	BP II	12.78	n	18	4	4
19	m	65	BP II	5.37	y	24	4	2
20	f	26	BP II	1.71	n	24	4	2
21	f	44	MD	5.02	y	12	5	2
22	m	53	BP I	4.50	n	18	4	3
23	m	41	BP II	7.09	y	12	3	3
24	f	30	MD	6.11	y	18	4	3
25	m	39	BP II	7.28	y	18	4	2

BP I = bipolar I disorder, BP II = bipolar II disorder, MD = major depressive disorder, CGI-S = Clinical Global Impression-Severity Scale scores (1 = normal, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = the most extremely ill)

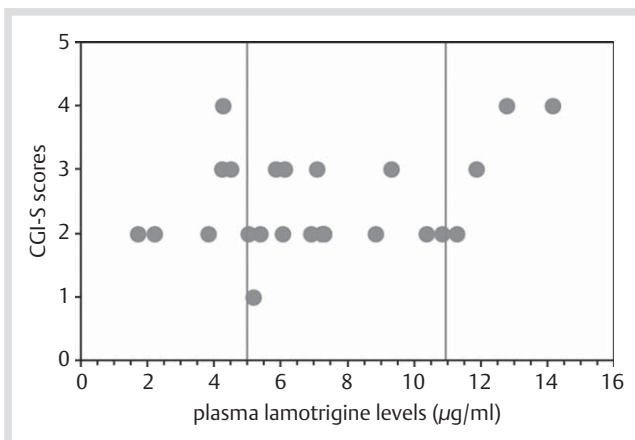


Fig. 1 The relationship between plasma lamotrigine levels and CGI-S scores at the last observation of 25 patients. 25 pairs of plasma lamotrigine levels and CGI-S scores were shown and the shape indicated the presence of the therapeutic window of lamotrigine as 5–11 µg/mL.

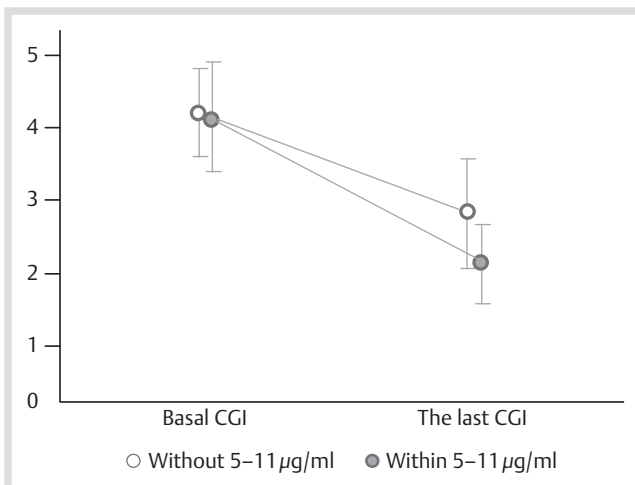


Fig. 2 The time course of basal CGI-S and the last CGI-S. The repeated measures of ANOVA revealed a significant tendency of the effect of the last lamotrigine levels.

Results

Table 1 shows patient demographics, lamotrigine levels and CGI-S scores in 25 patients. Fig. 1 shows the relationship between the last lamotrigine levels and the last CGI-S scores of 25 patients. Our visual inspection indicated the presence of a therapeutic window of lamotrigine from 5 to 11 µg/mL. Therefore, the following analyses were performed to use this range (5–11 µg/mL) as a potential therapeutic window.

The repeated measures of ANOVA revealed a significant tendency of the effect of the last lamotrigine levels (within 5–11 µg/mL or not) [lamotrigine, $F(1,23)=4.0$, $p=0.058$: CGI-S, $F(1,23)=57.6$, $p<0.0001$: lamotrigine \times CGI-S, $F(1,23)=2.2$, $p=0.16$] (Fig. 2).

The last CGI-S scores of the 15 patients whose lamotrigine levels were within 5–11 µg/mL were significantly lower than those of 10 patients whose lamotrigine levels were not within 5–11 µg/mL (2.2 ± 0.6 vs. 2.9 ± 0.9 , $t=2.45$, $p=0.023$). There were no significant differences in gender rate (6 females and 9 males within 5–11 µg/mL vs. 4 females and 6 males without 5–11 µg/mL, $p>0.99$), age (47.1 ± 12.8 years within 5–11 µg/mL vs. 41.6 ± 13.0 years without 5–11 µg/mL, $t=-1.04$, $p=0.31$), psychiatric

diagnoses (MD:BPI:BPPI; 4:1:10 within 5–11 µg/mL vs. 1:1:8 without 5–11 µg/mL, $p=0.59$) or lamotrigine administration period until the last observation (22.4 ± 12.5 months within 5–11 µg/mL vs. 22.2 ± 8.8 months without 5–11 µg/mL, $t=-0.042$, $p=0.97$).

Discussion

Our hypothesis that lamotrigine may have a therapeutic window for mood disorders was supported in the present study. The repeated measures of ANOVA failed to reach a significant level, but they reached a significant tendency. Moreover, the CGI-S scores at the last observation of the 15 patients whose lamotrigine levels were within 5–11 µg/mL were significantly lower than those of 10 patients whose lamotrigine levels were not within 5–11 µg/mL. Other factors were not significantly different between the groups. These findings suggest that 5–11 µg/mL may be therapeutic levels of lamotrigine effects for mood disorders.

Since the therapeutic levels of lamotrigine for epilepsy are reported to be 3–14 µg/mL [10], this range was also applied to our data. As a result, there were no significant findings (data not shown). Although a large part of our data were within 3–14 µg/mL, these findings suggest that 5–11 rather than 3–14 µg/mL may be more appropriate for the therapeutic levels of lamotrigine for mood disorders.

The main limitation is that this study was a retrospective naturalistic study. Further prospective studies are required which randomize patients to different doses and evaluate plasma levels and subsequent response over a defined period. Moreover, it is unclear whether antidepressant effect and/or prophylactic effect of lamotrigine were assessed by CGI-S and a CGI-S measure is a limited assessment. Moreover, CGI assessment was not blind to the hypothesis that lamotrigine may be helping the patients. Also, the analysis did not control for confounding variables including co-medications.

Conclusion

The present findings suggest that lamotrigine may have a therapeutic window for patients with mood disorder from 5 to 11 µg/mL.

Conflict of Interest

Terao T. has held grants and received honoraria for speaking or chairing educational meeting from GlaxoSmithKline. The other authors declare that they have no conflicts of interest.

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