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Research Article

UGT2B7 372A>G Polymorphism is related to a Therapeutic Response to Lamotrigine Augmentation Therapy in Depressed Patients Who Did Not Respond to Adequate Treatment: A Preliminary Study

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ABSTRACT

Purpose: Lamotrigine is mainly metabolized by *UGT1A4* and *UGT2B7*, both of which are expressed in the blood-brain barrier. Polymorphisms of said UDP-glucuronosyltransferases (*UGT*s) that affect enzyme activities have been reported. This study investigated the relationship between these polymorphisms and its therapeutic effect in 55 depressed patients who did not respond to adequate treatment during an 8-week treatment of lamotrigine augmentation using an open-study design.

Patients and Methods: The subjects were 55 depressed patients who had already shown insufficient response to at least 3 psychotropics including antidepressants, mood stabilizers, and atypical antipsychotics. The diagnoses were major depressive disorder (n=22), bipolar I disorder (n=9), and bipolar II disorder (n=24). The final doses of lamotrigine were 100 mg/d for 33 subjects who were not taking valproate and 75 mg/d for 22 subjects taking valproate, respectively. Depressive symptoms were evaluated by the Montgomery Åsberg Depression Rating Scale before and after the 8-week treatment. Blood sampling was performed at week 8. The genotypes of these polymorphisms were identified by Polymerase Chain Reaction (PCR).

Results: Percentage improvements at week 8 were significantly ($P<0.05$) higher in the patients with A/A genotype of *UGT2B7* 372A>G (48.8 ± 29.8%) than in those with A/G or G/G genotype (31.5 ± 27.6%). There was no significant relationship between the percent improvements and the *UGT1A4* 142T>G or *UGT2B7*-161C>T polymorphism.

Conclusion: The present study suggests that the *UGT2B7* 372A>G polymorphism may be partially related to a therapeutic response to lamotrigine augmentation therapy in depressed patients who did not respond to adequate treatment.

Keywords: Lamotrigine, *UGT2B7*, Genetic polymorphism, Augmentation therapy treatment-resistant

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INTRODUCTION

Lamotrigine is particularly useful in preventing depressive episodes of bipolar disorder (Geddes JR, *et al.*, 2009). A meta-analysis has demonstrated that lamotrigine possess therapeutic effects in improving unipolar and bipolar depressive symptoms (Solmi M, *et al.*, 2016). The authors of this study showed that lamotrigine augmentation may be effective in treatment-resistant depressive disorder, regardless of diagnosis for mood disoders (Kagawa S, *et al.*, 2010; Kagawa S, *et al.*, 2014). It was shown that lamotrigine is a useful augmentation of antidepressants for treatment-resistant unipolar depression in a meta-analysis (Goh KK, *et al.*, 2019). In addition, it was suggested that a better therapeutic response to lamotrigine as augmentation therapy was found in more severely depressed and more refractory patients than that seen with placebo in a double-blind placebo-controlled trial (Barbee JG, *et al.*, 2011). These findings indicate that lamotrigine augmentation can be one of the choices for some patients with treatment-resistant depressive disorder (Kagawa S, *et al.*, 2010; Kagawa S, *et al.*, 2014; Goh KK, *et al.*, 2019; Barbee JG, *et al.*, 2011).

Treatment-resistant depressed patients, who had a great number of mood episodes in the past and a short duration of present episodes, were likely to respond to lamotrigine augmentation therapy (Kagawa S, *et al.*, 2010). And, it has been demonstrated that a linear relationship exists between plasma lamotrigine concentrations and an early therapeutic response to lamotrigine augmentation therapy (Kagawa S, *et al.*, 2014) and that a therapeutic response to lamotrigine may be obtained at a plasma lamotrigine concentration of 12.7 μmol/L or higher (Kagawa S, *et al.*, 2014). An optimal dose of lamotrigine for augmentation therapy has been reported to be possibly determined on the basis of lamotrigine concentrations at week 2 (Nakamura A, *et al.*, 2016). Furthermore, a therapeutic response at week 8 could be predicted from a partial response at week 4 in the treatment of refractory depressed patients with lamotrigine augmentation therapy (Nagai G, *et al.*, 2017).

Lamotrigine is mainly metabolized by *UGT1A4*, and *UGT2B7*, which contribute to lamotrigine glucuronidation. Several mutated alleles of the *UGT1A4* and *UGT2B7* polymorphisms that affect the enzyme activities have been reported. However, the authors have shown that polymorphisms of *UGT1A4* 142T>G, *UGT2B7*-161C>T, and *UGT2B7* 372A>G do not affect the steady-state plasma concentrations of lamotrigine in patients with treatment-resistant depressive disorder receiving lamotrigine as augmentation therapy (Suzuki T, *et al.*, 2019). Meanwhile, both UGTs are also expressed in the blood-brain barrier (Ouzzine M, *et al.*, 2014) and may influence clinical response to lamotrigine by affecting its concentrations in the brain.

Therefore, the authors prospectively investigated the relationship between these polymorphisms and its therapeutic effect in depressed patients who did not respond to adequate treatment during an 8-week treatment of lamotrigine augmentation using an open-study design.

MATERIALS AND METHODS

Patients

The study was conducted at the University of the Ryukyus be-

tween April 2011 and February 2020. The present study originally included 60 Japanese depressed patients. The inclusion criteria were (a) diagnoses of major depressive disorder, bipolar I disorder, or bipolar II disorder according to the DSM-IV-TR criteria (American Psychiatric Association, 2000) (b) insufficient response to at least three psychotropics including antidepressants, mood stabilizers or atypical antipsychotics despite sufficient therapeutic doses and at least 4 weeks of treatment (c) a Montgomery Åsberg Depression Rating Scale (MADRS) score of 21 or more (Kagawa S, *et al.*, 2010; Kagawa S, *et al.*, 2014; Nakamura A, *et al.*, 2016; Nagai G, *et al.*, 2017; Suzuki T, *et al.*, 2019) (d) no previous treatment with lamotrigine (e) no lifetime history of substance abuse, organic brain syndrome, delirium or dementia (f) physically healthy without any clinically significant findings in clinical laboratory examinations, electrocardiography, and electroencephalography (g) no oral contraceptives in female patients. The study protocol was approved by the Ethics Committee of the University of the Ryukyus (No. 30). All patients had given a written informed consent to participate in this study.

Procedure

The medication of all subjects was unchanged for at least 4 weeks prior to the study. Antiepileptics inducing enzymes were excluded. After that, lamotrigine was co-given at 6 pm for 8 weeks as an augmentation therapy. The dose timing was chosen to avoid possible sedative effects. The mean ± SD of the number of psychotropic drugs co-administered with lamotrigine was 1.7 ± 0.6. These drugs were maintained during the study period. In case of 36 patients not given valproate, lamotrigine 25 mg/d was prescribed in the first 2 weeks, and the dose was incremented at the rate of 25 mg/2 weeks. As for the remaining 24 subjects given valproate, lamotrigine 25 mg/every other day was initiated during the first 2 weeks, the dose was incremented to 25 mg/d for the next 2 weeks, and thereafter at the rate of 25 mg/2 weeks. The final doses were 100 mg/d for the former and 75 mg/d for the latter, respectively. These doses were decided by a finding from Kagawa S, *et al.* indicating that a mean effective dose of lamotrigine was 88 mg/d in lamotrigine augmentation therapy (Kagawa S, *et al.*, 2014). No other medications were allowed, except for the occasional use of flunitrazepam (1-4 mg/d) as a hypnotic and sennoside (12-36 mg/d) as a laxative. Nursing staff or their families confirmed patients' adherence. Depressive symptoms were evaluated by the MADRS before and after the 8-week treatment. A responder was defined as a case with a final MADRS score of 10 or less. Spontaneously reported or observed adverse effects were reported during the study. Blood samplings were performed taken at 8 am after the 8th week of treatment.

Measurement tools

Genotyping data: DNA was isolated from peripheral leucocytes using a QIA-amp DNA Blood Maxi (Qiagen, Tokyo, Japan). The genotypes of *UGT1A4* 142T>G, *UGT2B7*-161C>T, and *UGT2B7* 372A>G were detected by real-time Polymerase Chain Reaction (PCR) methods according to Singkham N, *et al.*, 2013. The PCR conditions were 95°C for 10 minutes followed by 92°C for 15 seconds and 60°C for 90 seconds (Singkham N, *et al.*, 2013).

Lamotrigine concentration data: Plasma lamotrigine concentrations were measured using the high-performance liquid chromatography method reported by Brzaković BB, *et al.*, 2012. The detection limit was 0.04 μmol/L using 0.5 mL of plasma, and the coefficients of variation were 6.57 ± 2.01% for between-days and 4.95 ± 1.87% for within-day imprecision.

Statistical analyses

Analysis of variance was used to compare the percentage improvements at week 8 among the 3 diagnoses. The Wilcoxon rank-sum test was used to assess differences in the percentage improvements and plasma lamotrigine concentrations between two genotype groups of each polymorphism. The chi-square test was used to compare the number of responders at week 8 between two genotype groups of each polymorphism. A stepwise multiple regression analysis was applied to analyze the correlation between the percentage improvements and several factors including the three genetic polymorphisms, age, gender, duration of illness, number of previous mood episodes, duration of the present episode, entry MADRS score, valproate coadministration, and plasma lamotrigine concentrations, in which dummy variables were used for these polymorphisms (T/T=0; T/G G/G=1 for *UGT1A4* 142T>G polymorphism, C/C=0; C/T+T/T=1 for *UGT2B7*-161C>T polymorphism, and A/A=0; A/G+G/G=1 for *UGT2B7* 372A>G polymorphism), gender (male=0, female=1), and valproate coadministration (without=0, with=1). A two-tailed P value of less than 0.05 was regarded as statistically significant. SPSS 22.0 for Windows (SPSS, Japan Inc, Tokyo, Japan) was used to perform statistical analyses. Power analyses were performed with G*Power (Franz Faul, University of Kiel, Kiel, Germany) version 3.1.9.7.

RESULTS

Clinical characteristics and demographics of patients

Out of the 60 cases, two patients (1 male and 1 female) with bipolar I disorder withdrew from the study due to acute deterioration of depressive symptoms, two female patients with bipolar II disorder dropped out due to dizziness or lamotrigine-related rash, and 1 male patient with bipolar II disorder left from the study for treatment unrelated reasons. Thus, this study examined the remaining 55 subjects (39 females and 16 males; 37 in- and 18 out-patients) with the following diagnoses: Major depressive disorder (n=22), bipolar I disorder (n=9), and bipolar II disorder (n=24). 14 (25%) were smokers. The subjects' characteristics are listed in *Table 1*. The drugs prescribed (number of cases) prior to the introduction of lamotrigine were as follows: Paroxetine (10), mirtazapine (5), sertraline (3), trazodone (3), duloxetine (2), mianserin (2), amoxapine (1), clomipramine (1), escitalopram (1), milnacipran (1), setiptiline (1), and venlafaxine (1) in case of antidepressants; valproate (22), lithium (9), and clonazepam (5) in case of mood stabilizers; quetiapine (12), olanzapine (10), and aripiprazole (5) in case of atypical antipsychotics. These medications were given according to the attending psychiatrist independently of the study by considerations of the patient's symptomatology and concerns about adverse effects. Thus, there was no specific reason for the highest number of valproate coadministration. There were no differences in the percentage improvements or the number of responders at week 8 among major depressive disorder (39.4 ± 38.6%, 6/22), bipolar I disorder (46.9 ± 36.6%, 5/9), and bipolar II disorder (44.0 ± 29.7%, 9/24).

Comparison of the therapeutic response with the UGT polymorphisms

Table 2 shows the number of genotype groups, the mean ± SD of the percentage improvements, the numbers of responders, and plasma concentrations of lamotrigine. Percentage improvements at week 8 and the number of responders were significantly (P<0.05 and P<0.05) higher in the patients with A/A genotype of *UGT2B7* 372A>G than in those with A/G or G/G genotype. There were no significant differences in the mean percentage improvements or the number of responders between the two genotype groups of the other genetic polymorphisms (*UGT1A4* 142T>G and *UGT2B7*-161C>T). No significant differences were found in the mean plasma lamotrigine concentrations between the two genotype groups of each polymorphism. The statistical power for *UGT1A4* 142T>G, *UGT2B7*-161C>T, and *UGT2B7* 372A>G polymorphisms were calculated to be 6%, 20%, and 56% to detect a medium effect size (0.50, alpha=0.05), respectively.

A stepwise multiple regression analysis showed that the *UGT2B7* 372A>G polymorphism and plasma lamotrigine concentrations had significant (P<0.05 and P<0.001) effects on the percentage improvements *(Table 3)*.

Table 1: Clinical characteristics and demographics of patients

Clinical characteristics	Subjects (n=55)
Age (years)	44.9 ± 14.7
Gender (n)	
Male	16
Female	39
Body weight (kg)	60.0 ± 14.4
Duration of the present depressive episode (months)	28.2 ± 53.3
Number of previous mood episodes	3.1 ± 3.5
Number of past ineffective medications	6.0 ± 2.6
Baseline Montgomery Åsberg Depression Rating Scale (MADRS) score	26.3 ± 5.4
Note: Values are expressed as mean ± SD or as stated	

Table 2: Influences of *UGT1A4* 142T>G, *UGT2B7*-161C>T, and *UGT2B7* 372A>G polymorphisms on the percentage improvement, the number of responders, and plasma lamotrigine concentration

Genotype group	n	Percentage improvement (%)	Number of responders (n)	Lamotrigine (μmol/L)
UGT1A4 142T>G				
T/T	38	42.5 ± 31.1	13	12.8 ± 7.2
T/G+G/G	17	39.5 ± 27.9	7	13.3 ± 8.0
UGT2B7-161C>T				
C/C	33	45.4 ± 30.7	12	12.7 ± 5.7
C/T+T/T	22	35.8 ± 28.3	8	13.4 ± 9.4
UGT2B7 372A>G				
A/A	32	48.8 ± 29.8*	16*	13.0 ± 8.5
A/G+G/G	23	31.5 ± 27.6	4	13.0 ± 5.5
Note: Values are expressed as mean ± SD or as stated. *P<0.05 compared with A/G+G/G				

Table 3: Standardized partial regression coefficients and multiple correlation coefficients in multiple regression analysis of the percentage improvement

Variables	Standardized partial regression coefficients	P
UGT2B7 372A>G genotype	-0.262	<0.05
Plasma lamotrigine concentration	0.347	<0.01
Multiple correlation coefficient	0.44	<0.005

DISCUSSION

The patients with the A/A genotype of the *UGT2B7* 372A>G showed higher percentage improvements than those with the A/G or G/G genotype. Moreover, the finding was confirmed by multiple regression analysis. The number of responders was higher in the former than in the latter. These results suggest that the A/A genotype of the *UGT2B7* 372A>G may be partially related to a good therapeutic response to lamotrigine augmentation therapy in depressed patients who did not respond to adequate treatment. The authors have shown that the *UGT2B7* 372A>G polymorphism does not affect the steady-state plasma concentrations of lamotrigine in patients with treatment-resistant depressive disorder receiving lamotrigine as augmentation therapy (Suzuki T, *et al.*, 2019). The identical finding was observed in this study. However, the UGT is also expressed in the blood-brain barrier (Ouzzine M, *et al.*, 2014). Milosheska D, *et al.*, 2016 have demonstrated that clearance of lamotrigine is high in patients with the G allele of the *UGT2B7* 372A>G. The *UGT2B7* expression was found in the brain, and may play important role in the metabolism of morphine (King CD, *et al.*, 1999). It is likely that in patients with the G allele, *UGT2B7* expressed in the blood-brain barrier that has increased enzyme activity may attenuate therapeutic effects of lamotrigine by metabolizing the drug in the brain rapidly, although there is no direct evidence that the glucuronidation is a known way of lamotrigine metabolism in the brain.

There were no significant differences in the mean percentage improvements or the number of responders between the two genotype groups of *UGT1A4* 142T>G or *UGT2B7*-161C>T. The result suggests that the two polymorphisms are not associated with a therapeutic effect of lamotrigine augmentation therapy. The reasons for the discrepancy remain unclear. Singkham N, *et al.*, 2013 reported that lamotrigine clearance in patient carrying the *UGT2B7*-161 C/T or T/T genotype was 18% lower than that in those carrying C/C genotype, which was confirmed by Milosheska D, *et al.*, 2016. Two previous studies showed that patients with G/G or G/T genotype of the *UGT1A4* 142T>G reduced serum lamotrigine concentration by about 50% compared with those with T/T genotype (Gulcebi MI, *et al.*, 2011; Chang Y, *et al.*, 2014). Meanwhile, it has been shown that the clearance of lamotrigine was 117% higher in patients with G/G genotype of the *UGT2B7* 372A>G compared with those with A/A genotype (Milosheska D, *et al.*, 2016). Therefore, the negative relationship may be due to the possibility that the influences of the *UGT1A4* 142T>G or *UGT2B7*-161C>T polymorphism on the enzyme activity might be relatively modest, although no studies have directly compared the effect of the three polymorphisms on lamotrigine metabolism.

This study has several limitations. First, both bipolar and unipolar depressed patients were combined. Second, the patients were heterogeneous in duration of illness, number of previous mood episodes, and duration of the present depressive episodes. Third, the psychotropics to which the

subjects had not responded and the co-administered drugs varied among the subjects. These drugs might have influenced therapeutic response or said UGT enzyme activity. Fourth, the influences of drugs, which induce UGT enzyme activity, such as carbamazepine or phenytoin, were not studied. Fifth, smoking might affect the enzyme activity in relation to these polymorphisms. Sixth, the results may not be applied to other clinical settings, because the subjects did not respond to adequate treatment, and lamotrigine was administered as an augmentation strategy. Seventh, spontaneous remission might be observed in the study period. Eighth, the small sample size did not allow to draw a definitive conclusion. Also, the possibility of type II error cannot be ruled out because of the low power. Therefore, a further precise and well-controlled study considering these problems should be conducted with a larger number of homogeneous subjects.

CONCLUSION

The patients with the A/A genotype of the *UGT2B7* 372A>G showed higher percentage improvements than those with the A/G or G/G genotype. Moreover, the finding was confirmed by multiple regression analysis. The present study concludes that there was no significant relationship between the percent improvements and the *UGT1A4* 142T>G or *UGT2B7*-161C>T polymorphism. This study suggests that the *UGT2B7* 372A>G polymorphism may be partially related to a therapeutic response to lamotrigine augmentation therapy in depressed patients who did not respond to adequate treatment.

DECLARATIONS

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