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The Valproate Serum Level in Maintenance Therapy for Bipolar Disorder in Japan

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ABSTRACT

The appropriate therapeutic serum valproate level in maintenance therapy for bipolar disorder is not well known. We studied the serum valproate levels in seventeen bipolar I and twenty-four bipolar II disorder outpatients who had been treated with stable doses of valproate successfully for at least 12 months as prophylactic therapy. The trough serum valproate levels were 52.2 ± 20.4 μg/ml in bipolar I, and 41.0 ± 18.3 μg/ml in bipolar II disorder patients, respectively. A greater trend towards a higher trough level (p=0.07) was indicated in the bipolar I disorder group. We speculate that these valproate levels may be an approximation to the appropriate valproate levels in maintenance therapy and that there may be a correlation between the level of valproate required for stabilization and the subtype of the bipolar disorder. However, when interpreting these findings, certain limitations to this study?need to be taken into account as follows. The sample size was small. We could not look at a group on valproate that had relapsed and a group that had dropped out of maintenance therapy. Further studies are needed.

Key words: *Valproate, Serum valproate level, Bipolar disorder, Maintenance therapy*

Bipolar disorder, historically known as manic-depressive disorder, is a psychiatric diagnosis defined by the presence of one or more manic episodes with or without one or more depressive episodes. The effect of valproate on acute mania has already been clarified and valproate is the first-line drug for acute mania[12,13)]. The efficacy of valproate in maintenance therapy for bipolar disorder is still not well established[4)]. However, in a clinical setting, valproate has been used in maintenance therapy for bipolar disorder. Some algorithms and guidelines recommend the use of valproate during the maintenance phase[6)].

The appropriate therapeutic serum valproate level in maintenance therapy for bipolar disorder is not well known. In acute mania, the target serum valproate level for a best response was above 94 μg/ml[1)]. For maintenance therapy, Keck et al[11)] indicated that patients with serum valproate levels between 75 and 99 μg/ml provided significantly better outcomes than patients with either lower or higher levels. Recently, we demonstrated that continuing a high-dose of valproate may cause adverse effects in Japanese bipolar disorder patients and that the dose of valproate may need to be decreased when acute mania is in remission[15)]. Bowden[3)] reported that serum valproate levels above 125 μg/ml were associated with greater adverse effects. For successful maintenance therapy, ensuring adherence to

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medication is necessary. Adverse effects are a major cause of poor adherence to medication. Some guidelines recommend lifetime treatment with a mood stabilizer, especially for patients with recurrent bipolar disorder or for patients with a family history[6]. To continue the maintenance therapy for a sufficient duration, the serum valproate level should be adjusted so that it causes few adverse effects. If the serum level is too low, a relapse may occur, and if the serum level is too high, the maintenance therapy may not be tolerated (patients may drop out because of the adverse effects induced by high dose valproate). However, the most appropriate therapeutic serum valproate level is still not known.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) recognizes two types of bipolar disorders – bipolar I and bipolar II[2]. People with bipolar I disorder suffer from at least one manic or mixed episode, and may experience depressive episodes. On the other hand, people with bipolar II disorder experience a milder form of manic episode, known as a hypomanic episode as well as major depressive episodes. Although bipolar II is thought to be less severe than bipolar I with regard to symptom intensity, it is actually severer and more distressing with respect to episode frequency and overall course[9,10]. It is also not widely known that there is discrepancy in the appropriate therapeutic serum valproate levels between bipolar I disorder and bipolar II disorder. Jacobsen[8] reported that there might be a correlation between the severity of bipolar disorder and the serum valproate level required for stabilization, and that milder forms of bipolar cycling may require lower doses of valproate.

Thus, conflicting views exist at the present time regarding the appropriate therapeutic level of valproate in maintenance therapy for bipolar disorder. In this study, we examined the serum valproate levels in bipolar I and II disorder outpatients who had been treated successfully with stable doses of valproate as a prophylactic therapy for at least twelve months at several medical institutions. We predicted that the serum valproate levels in these subjects might be relatively low and that adverse effects might be few. We also hypothesized that there would be discrepancies in the data for appropriate serum valproate levels in maintenance therapy between the different subtypes of bipolar disorder.

SUBJECTS AND METHODS

Study Design

This study was a retrospective chart review of naturalistic clinical treatment for bipolar disorder with valproate at several medical institutions.

Patients

Subjects included in this study were outpatients diagnosed as having bipolar disorder by clinical assessment using the DSM-IV criteria[2] at Hiroshima University Hospital, Hokkaido University Hospital, Hiroshima City Hospital, University Hospital of Occupational and Environmental Health, and Tokushima University Hospital, who were treated successfully with valproate for acute episodes (depressive episodes, manic episodes) as assessed by the clinical global impressions scale for bipolar disorder (CGI-BP)[16] retrospectively, and also successfully treated with almost stable doses of valproate successfully for at least 12 months as prophylactic therapy. Patients were excluded if they were co-administrated with lithium and/or with carbamazepine. Lamotrigine is not authorized for clinical use in Japan. Patients with poor adherence to medication were also excluded. Patients co-administrated with neuroleptics and/or anti-depressants were not excluded. It is a study of pre-existing data in which informed consent could be waived.

Assessment

We investigated the most recent serum valproate level. However, laboratory serum sampling times were random. Administration times and schedules varied in each patient. In addition, valproate was administered orally as a syrup, as a powder, or in tablet form, including slow-acting drugs. As a result, we needed to estimate the peak and trough serum concentrations of valproate for each patient. These concentrations were estimated by Bayesian estimation[14] with a software package, VCM-TDM E_ edition, ver. 2.04 for Windows (Shionogi & Co., Ltd., Osaka, Japan)[18], using the population pharmacokinetic parameters of valproate obtained from Japanese patients[7,17]. To estimate the trough and peak serum concentrations of valproate, we investigated the demographic and clinical data for each patient, including age, actual body weight and height, dates and times of valproate administration, serum valproate levels, laboratory serum sampling times, daily dosage of valproate, duration of stable doses of valproate, formulations of valproate, and adverse effects.

Data Analysis

We compared the demographic variables between bipolar I disorder (BP-I) patients and bipolar II disorder (BP-II) patients. The unpaired t-test and the x^2 test were used for statistical comparisons. The results were expressed as mean ± standard deviation, and the significance level was set at $p < 0.05$.

RESULTS

The number of subjects of this study was forty-one. Their demographic characteristics are shown in Table 1. The mean dosage of valproate was 731.7 ± 315.0 mg/day. The mean dosage per weight was 12.4 ± 4.8 mg/kg/day. The mean duration of almost stable doses of valproate was 40.8 ± 32.4 months. The mean

Table 1. Characteristics of subjects

		Mean ± SD	max	Min
Age		51.0 ± 14.6	79	22
Sex, No. (%)				
Male	17 (41)			
Female	24 (59)			
DSM-IV, No. (%)				
BP-I	17 (41)			
BP-II	24 (59)			
Valproate				
Dosage (mg/day)		731.7 ± 315.0	1400	200
Dosage/weight (mg/kg/day)		12.4 ± 4.8	23.5	3.3
Duration of stable doses (months)		40.8 ± 32.4	152	12
Serum level(μg/ml)				
Sampling [a]		52.1 ± 21.2	95	13
Trough [b]		45.6 ± 19.8	91	12
Peak [b]		61.3 ± 25.1	128	15
Co-administrated medication, No. (includes duplication)	21			
Neuroleptics				
Aripiprazole	0			
olanzapine	3			
quetiapine	3			
risperidone	0			
others	5			
Antidepressants				
SSRIs	3			
SNRIs	2			
TCAs	7			
others	4			

The results were expressed as mean ± standard deviation.
[a] We investigated the most recent serum valproate level. Because all subjects were outpatients, laboratory serum sampling times were random.
[b] The trough and peak serum concentrations of valproate for each patient were estimated by Bayesian estimation[14] with a software package, VCM-TDM E_edition, ver. 2.04 for Windows (Shionogi & Co., Ltd., Osaka, Japan)[18], using the population pharmacokinetic parameters of valproate obtained from Japanese patients[7, 17].
Abbreviations: BP-I = bipolar I disorder, Bp-II = bipolar II disorder, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin noradrenaline reuptake inhibitor, TCA = tricyclic antidepressant

sampling serum valproate level was 52.1 ± 21.2 μg/ml. The trough and peak serum levels of valproate predicted by a Bayesian approach were 45.6 ± 19.8 μg/ml and 61.3 ± 25.1 μg/ml, respectively. The number of subjects who were co-administrated with antidepressants and/or neuroleptics was twenty-one. The details are shown in Table 1.

The demographic characteristics of BP-I patients and of BP-II patients are shown in Table 2. The proportion of female subjects in this study tended to be higher in the BP-II group compared with the BP-I group ($p = 0.060$). The dosage ($p < 0.01$) and the dosage per weight ($p < 0.03$) of the BP-I group were higher than those of the BP-II group (unpaired *t*-test).

Table 2. Characteristics and clinical data Comparison of BP-I and BP-II

		BP-I mean ± SD (n = 17)	BP-II mean ± SD (n = 24)	p Value [a]
Age		49.3 ± 17.8	52.2 ± 12.2	.568
Sex, No. (%)				
Male		10 (59)	7 (29)	.060*[b]
Female		7 (41)	17 (71)	
Valproate				
Dosage (mg/day)		911.8 ± 327.6***	604.2 ± 238.6	.001*
Dosage/weight (mg/kg/day)		14.3 ± 4.5**	11.1 ± 4.6	.029*
Duration of stable doses(months)		38.4 ± 34.4	42.6 ± 31.6	.686
Serum level(μg/ml)				
Sampling [b]		57.1 ± 19.4	48.6 ± 22.2	.212
Trough [c]		52.2 ± 20.4	41.0 ± 18.3	.073*
Peak [c]		68.6 ± 25.9	56.2 ± 23.8	.122
Adverse effects, No. (%)	+	5 (29)	6 (25)	.761
	–	12 (71)	18 (75)	

The results were expressed as mean ± standard deviation.
[a] The unpaired t-test was used for statistical comparisons. The x^2 statistic was used for categorical measures. Results at trend level or greater are indicated by an asterisk (*); p values significant at < .05 are indicated with boldface.
[b] We investigated the most recent serum valproate level. Because all the subjects were outpatients, laboratory serum sampling times were random.
[c] The trough and peak serum concentrations of valproate for each patient were estimated by Bayesian estimation[14] with a software package, VCM-TDM E_edition, ver. 2.04 for Windows (Shionogi & Co., Ltd., Osaka, Japan)[18], using the population pharmacokinetic parameters of valproate obtained from Japanese patients[7, 17].
Abbreviations: BP-I = bipolar I disorder, Bp-II = bipolar II disorder

Table 3. Treatment-emergent adverse effects at the time of research

	No. (%)
Sedation	8 (20)
Hyperammonemia	2 (5)
Thirst	2 (5)
Weight gain	1 (2)
Liver dysfunction	1 (2)

The duration of stable doses of valproate was not significantly different between the two groups (p = 0.686). The sampling serum valproate level (p = 0.212) and the peak serum level (p = 0.122) were not significantly different between the two groups. On the other hand, the trough level tended to be higher in the BP-I group than in the BP-II group (p = 0.073). With respect to the presence/absence of adverse effects, no difference was noted between the two groups.

Treatment-emergent adverse effects at the time of research are shown in Table 3. Sedation was the most common adverse effect.

DISCUSSION

In regard to valproate, it is difficult to maintain serum levels within a therapeutic range because of its short biological half-life. Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations among individuals. Population pharmacokinetics seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified. A pharmacokinetic analysis software, which includes an individual pharmacokinetic parameter estimation based on the Bayesian forecasting method and calculation of recommended dosage schedule, was

developed for use in clinical practice. In this study, we investigated the most recent serum valproate level. However, laboratory serum sampling times were random, and administration times and schedules varied for each patient. In addition, valproate was administered orally as a syrup, as a powder, or in tablet form, including slow- acting drugs. Therefore, we need to estimate the peak and trough serum concentrations of valproate for each patient. These concentrations were estimated by Bayesian estimation

The appropriate therapeutic valproate serum level in maintenance therapy for bipolar disorder is not well known. Allen et al[1] reported that the target blood level of valproate for a best response was above 94 μg/ml in acute mania. There is no evidence that this blood level is also appropriate for a prophylactic effect. Recently, we demonstrated that continuing high doses of valproate may cause adverse effects in Japanese patients with bipolar disorder and that the dose of valproate may need to be decreased after remission[15]. In this study, the mean sampling serum valproate level was 52.1 μg/ml. This was relatively low compared with the target blood level in acute mania as reported by Allen et al[1].

The dosage and the dosage per weight in the BP-I group were significantly higher than in the BP-II group. The trough serum levels also tended to be higher in the BP-I group than in the BP-II group, but this was not statistically significant. There may be a correlation between the blood level of valproate required for stabilization and the subtype of the bipolar disorder. Jacobsen[8] reported that many cyclothymia and milder rapid cycling bipolar disorder patients were maintained on low-dose valproate for substantial lengths of time without recurrence of affective symptomatology. It was also reported that there might be a correlation between the severity of bipolar disorder and the blood level of valproate required for stabilization, and that milder forms of bipolar cycling might require lower doses of valproate. Our findings are in accord with these conclusions. As subjects of this study, the proportion of females tended to be higher in the BP-II group compared with the BP-I group. The reason is unknown. However, this result is consistent with the prevalence of bipolar disorder. The prevalence of BP-I is believed to be similar between men and women, but BP-II occurs more frequently in women[5].

Ensuring adherence to medication is necessary for successful maintenance therapy for bipolar disorder. Adverse effects are one of major causes of poor adherence to medication. The lower the serum level, the more frequently a relapse occurs. If the tolerability is unsatisfactory, the dosage of valproate should be decreased to prevent drop out from the maintenance therapy. The serum valproate should be adjusted not only to prevent relapses but also to provide satisfactory tolerability for patients. However, the most appropriate therapeutic level of valproate is still not known. In this study, the trough serum valproate levels of Japanese BP-I and BP-II patients success-fully treated with valproate as a long-term prophylactic therapy were 52 μg/ml and 41 μg/ml, respectively. We speculate that these levels may be an approximation to the most appropriate valproate levels in maintenance therapy with regard to continuing successful prophylactic therapy because, firstly, relapse is prevented for an extended period and, secondly, long-term continuation of treatment is possible due to remarkable tolerability. However, when interpreting these findings, certain limitations to this study need to be taken into account. The sample size was small, and this study was not a control trial. There is also some weakness in the discussion of the optimal serum valproate level in maintenance therapy for bipolar disorder adequately because of its retrospective chart review. We were unable to examine, by way of comparison, a group on valproate that had relapsed, one with lower valproate levels perhaps. In addition, we were unable to examine a group (possibly one with higher valproate levels) that had dropped out of maintenance treatment. Patients were given a variety of drug combinations including neuroleptics and antidepressants, so we were unable to draw a conclusion that these prophylactic effects were caused only by valproate.

Further studies are needed. For example, a comparison of long-term relapse prevention in BP-I patients and BP-II patients among groups with low, middle, and high serum valproate levels is necessary. The results of this study may be important as preliminary data for future research.

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