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Clinical response of quetiapine in rapid cycling manic bipolar patients and lactate level changes in proton magnetic resonance spectroscopy

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Abstract

The aim of the current study was to evaluate the relationship between quetiapine's effect on the improvement of mood symptoms in bipolar patients and brain metabolite level changes as measured by proton magnetic resonance spectroscopy (¹H-MRS). Rapid cycling bipolar patients in the manic state were recruited and treated with quetiapine for 12 weeks. Clinical assessment was performed using the Young Mania Rating Scale (YMRS), the 17-item Hamilton Depression Rating Scale (HDRS) and the Clinical Global Impression-Severity scale (CGI-S) at baseline and weekly intervals during the 12-week period. In order to evaluate metabolite level changes over time, ¹H-MRS scans were acquired at baseline and week 12. There were significant reductions in YMRS scores (by 43.0%), HDRS scores (by 27.5%) and CGI-S score (by 44.6%) over the 12 week-period. Lactate levels significantly decreased over the 12-week study period (22.4%). This change in lactate levels was more prominent in quetiapine responders than in non-responders. Additionally, there was a positive correlation between changes in lactate levels and those in YMRS scores ($r=0.52$, $p=0.003$). Our findings suggest that quetiapine's antimanic and antidepressant efficacy in patients with rapid cycling bipolar disorder may potentially be related to decreased lactate levels in frontal regions of the brain.

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Keywords

bipolar disorder; lactate; magnetic resonance spectroscopy; quetiapine

1. INTRODUCTION

Individuals with rapid cycling bipolar disorder, defined as four or more episodes in the previous 12 months (DSM-IV-TR)(APA 2000), constitute approximately 20% of those with bipolar disorder (Calabrese et al., 2000). Since subjects with rapid cycling bipolar disorders have, in general, a poor response to conventional mood stabilizers such as lithium and carbamazepine (Okuma, 1993), treatment with atypical antipsychotics has emerged as an important alternative treatment strategy for these patients (Sanger et al., 2003; Vieta et al., 1998; Vieta et al., 2002). Among these agents, quetiapine has been suggested as a useful therapy for treatment-resistant bipolar disorder, including the rapid cycling type (Dunayevich and Strakowski, 2000; Ghaemi and Katzow, 1999; Vieta et al., 2002). Vieta and colleagues (2002) have reported that the addition of quetiapine to ongoing treatment of lithium, valproic acid and/or carbamazepine is effective for managing manic symptoms in rapid cycling bipolar patients. However, the mechanism by which quetiapine exerts a mood stabilizing effect remains to be clarified.

There have been several magnetic resonance spectroscopy (MRS) studies in bipolar patients reporting abnormalities in levels of metabolites including lactate, Glx (the combined signal for glutamate, glutamine and gamma-aminobutyric acid), and *myo*-inositol (Dager et al., 2004; Friedman et al., 2004). Among these, changes in lactate levels are worthy of special note, since increased lactate level has been closely related to a hypothesized mitochondrial dysfunction in bipolar disorder. Mitochondrial dysfunction of the central nervous system--in particular, a shift from oxidative phosphorylation toward glycolysis--has been suggested as one of core features of bipolar pathophysiology (Kato and Kato, 2000; Stork and Renshaw, 2005). In this context, Dager and colleagues (2004) have reported in a proton (¹H) MRS that the lactate level is increased in medication-free subjects with bipolar depression.

Recently, Atmaca and colleagues (2007) have reported that bipolar subjects treated with quetiapine and valproate demonstrated higher NAA/CHO ratios than those treated with valproate monotherapy in a cross-sectional study design.

In the present study, we conducted a 12-week open-label study to evaluate the relationship between the potential efficacy of quetiapine monotherapy in patients with rapid cycling bipolar disorder and brain metabolite level changes as measured by ¹H-MRS. We hypothesized that quetiapine-treated patients would show a decrease in cerebral lactate levels. We also hypothesized that this change, if observed, would correlate with mood symptom improvement in rapid cycling bipolar subjects.

2. METHODS

2.1. Subjects

Patients with rapid cycling bipolar disorder were enrolled. Inclusion criteria were 1) age range: 20–60 years old, 2) both sexes, 3) DSM-IV bipolar disorder, as determined by the Structured Clinical Interview for DSM-IV–Patient Version (SCID–P)(First et al., 1995), 4) rapid cycling subtype, with a minimum of four mood episodes a month in the previous 12 months prior to enrollment, 5) current manic episode with the Young Mania Rating Scale (Young et al., 1978) score of 20 or greater. Exclusion criteria included 1) major medical or neurological disorders, 2) active substance abuse in the preceding 3 months, 3) contraindications to magnetic resonance imaging including pregnancy and metal implants, 4) comorbid axis I psychiatric

diagnosis requiring psychotropic medications, and 5) comorbid antisocial and borderline personality disorders.

This study was approved by the Institutional Review Board at the Seoul National University Hospital. A protection policy for study subjects, including written informed consents, an ethics code and other regulatory considerations was strictly followed. Forty-five patients gave their informed consent before screening procedures for inclusion in the study, in accordance with guidelines laid down in the Declaration of Helsinki.

A minimum two-day washout period for psychotropic medications was required. Twenty one subjects treated with mood stabilizers immediately before entering the study underwent a mean 3.0 day (SD: 1.7 and range: 2–8 days) washout period. During this washout period, treatment with benzodiazepine was allowed for managing agitation and behavior control.

Quetiapine dosing started with 25mg twice a day for two days, then 50mg twice a day for two days, and 100mg twice a day thereafter. From day 6 and 8 until the end of the study period, an additional amount up to a total of 400mg per day was allowed and adjusted at the discretion of the clinician according to the patients' improvement and tolerance, with flexible dosing. Patients received a mean dose of 384.3 mg per day (SD: 29.1) by day 14 of treatment, but by the end of study period at week 12 their average dose of quetiapine was reduced to 261.7 mg/day (SD 72.7). The mean modal dose was 308.3 mg per day (SD: 49.3).

No other psychotropic medications were prescribed except for benzodiazepines for managing agitation and behavior control. These were administered in doses equivalent to less than 20 mg of diazepam per day during the washout and treatment periods

2.2. Clinical assessment

The Young Mania Rating Scale (YMRS)(Young et al., 1978), the 17-item Hamilton Depression Rating Scale (HDRS)(Hamilton, 1960), and the Clinical Global Impression-Severity scale (CGI-S)(Guy, 1976) were administered at baseline and at weekly intervals during the 12-week study period. Changes in mean YMRS total scores served as the primary outcome measure. Secondary efficacy measures were changes in mean HDRS and CGI-S total scores. *A priori*, treatment response was defined as the 50% or greater of reduction of YMRS scores. Remission was defined by an endpoint YMRS score of 12 or lower.

Adverse events were assessed by open-ended, non-leading questions at every visit from week 1 to week 12. Safety and tolerability were evaluated by assessing adverse events and withdrawal due to adverse events.

2.3. Magnetic resonance imaging (MRI)

Brain MRI was performed using a 3 Tesla GE whole body imaging system (GE VH/i, USA). A three-dimensional spoiled gradient (SPGR) echo pulse sequence was used to produce 248 0.7-mm-thick contiguous sagittal images (echo time [TE]=14 msec, repetition time [TR]=5.7 msec, inversion time [TI]=400 ms, 256 × 256 matrix; field of view [FOV]=22 cm, flip angle=20°, 1 number of excitation [NEX]).

Axial T-2 weighted images (TE=118 msec, TR=3,500 msec, 256 × 192 matrix; FOV=22cm, flip angle=90°, 3 NEX, 5-mm-thick slices, 1.5 mm skip) as well as Fluid Attenuated Inversion Recovery (FLAIR) axial images (TE=145 msec, TR=9,900 msec, TI=2,250 msec, 256 × 192 matrix; FOV=22 cm, flip angle=90°, 1 NEX, 5-mm-thick slices, 1.5 mm skip) were obtained to screen for gross qualitative structural abnormalities.

2.4. Proton magnetic resonance spectroscopy (¹H-MRS) and voxel-of-interest (VOI) placement of the midfrontal gray matter

Patients received two ¹H-MRS scans at baseline and week 12 of treatment, to be assessed regarding changes in brain metabolite levels over time.

Localized point resolved spectroscopy (PRESS) pulse sequence was performed using a single-voxel ¹H-MRS obtained by a quadrature head coil on a 3 Tesla whole body MR scanner (GE VH/i, USA). Measurement parameters were as follows; TE=35 msec, TR=2,000 msec, phase-cycling=8, voxel of interest (VOI)=15 × 15 × 15 mm, acquisition time=128 × 2 sec, bandwidth=2,500 Hz.

Brain voxels of interest were chosen in the midfrontal gray matter from the axial plane by a skilled radiologist (figure 1). This VOI was selected in the midline including both left and right frontal gray matter. In the axial slice visualizing the most anterior boundary of the callosal genu, VOI was located nearest to the callosal genu and centered on the interhemispheric fissure, covering the bilateral anterior cingulate gray matter, as previously described (Yamasue et al., 2002). For the midfrontal gray matter VOI, in order to correct for the differences in brain tissue and cerebrospinal fluid (CSF) composition, segmentation was performed on the VOI on T1 images. Composition of the brain tissue and CSF were 96.2±1.9 and 4.8±2.3 %.

Absolute concentrations of n-acetyl-aspartate (NAA), choline, creatine (Cr) and *myo*-inositol, lactate, and Glx were estimated for VOIs using LCModel software (Provencher, 1993), with the unsuppressed water signal as an internal reference. The standard GE libraries of model metabolite spectra provided with the LCModel were used as a basis set. Metabolite levels were calculated in mM level.

2.5. Statistical analysis

Data were analyzed for an intent-to-treat population (ITT, n=38). The last observation carried forward (LOCF) method was used for analysis of variance (ANOVA) for repeated measures, followed by planned comparisons. Changes in brain metabolite levels over time were compared from baseline to exit in subjects who completed the 12-week study (n=30). Paired t-tests were performed for an analysis of effectiveness measures where appropriate.

Comparison of metabolite levels between responders and non-responders was conducted in order to evaluate whether clinical responses due to quetiapine are potentially related to changes in brain metabolite levels. In addition, we conducted subgroup analyses between subjects with and without psychotic features in order to determine whether subjects' clinical features are associated with brain metabolites changes following quetiapine treatment. In light of the small sample size these analyses were conducted using the Mann-Whitney U-test. Correlations between changes in clinical variables and metabolite levels were evaluated using the Pearson correlation analysis. Statistical significance was defined at an alpha level of 0.05 or less and two-tailed. Statistica 7.1 for Windows (StatSoft, Tulsa, OK, 2005) was used for all computations.

3. RESULTS

3.1. Demographic characteristics

Out of forty-five patients who consented to participate, three were excluded due to recent active substance abuse (n=2) and comorbid borderline personality disorder (n=1). Safety data were analyzed for all 42 subjects who enrolled in the study. Of these, 38 had at least one assessment and were included in analyses for efficacy in ITT populations. Demographic and clinical information at baseline are presented in Table 1.

Thirty (78.9%) of the study participants completed the 12-week study. Three, one, two, and two patients dropped out at weeks 2, 3, 4, and 7, respectively. Reasons for non-completion were loss to follow-up (n=3) and noncompliance (n=5). There were no significant differences between the completer and non-completer groups with regard to age, sex composition, and baseline measurements for the YMRS, HDRS and CGI-S scores [$t(36)=-0.72$, $p=0.48$; $\chi^2(1)=1.23$, $p=0.27$; $t(36)=0.98$, $p=0.3$; $t(36)=1.83$, $p=0.08$ and $t(36)=-1.23$, $p=0.23$, respectively].

3.2. Clinical efficacy

Results of repeated measures ANOVA for efficacy measures are presented in Figure 2. There were significant improvements in YMRS, HDRS and CGI-S mean scores through the 12-week study period [$F(12, 444)=27.7$, $p<0.001$; $F(12, 444)=23.9$, $p<0.001$ and $F(12, 444)=97.6$, $p<0.001$]. Planned comparisons showed that YMRS, HDRS and CGI-S scores at endpoint were significantly greater than those at baseline ($t=-10.1$, $p<0.001$; $t=-8.69$, $p<0.001$ and $t=-13.6$, $p<0.001$, respectively). Moreover, significant improvements in YMRS, HDRS and CGI-S scores at 1 week were observed by using planned comparisons ($t=-3.10$, $p=0.004$; $t=-4.77$, $p<0.001$ and $t=-3.15$, $p=0.003$, respectively). 34.2% and 15.8% of patients demonstrated the treatment response and the remission, respectively.

3.3. Proton magnetic resonance spectroscopy (1H-MRS)

Bipolar subjects had a decrease in lactate levels in the midfrontal gray matter over the 12-week period [$t(29)=15.4$, $p<0.001$, by 22.4 %]. Responders (n=9) showed a significantly greater decrease in the lactate levels relative to non-responders (n=21; $z=-2.08$, $p=0.037$, 26.9% vs. 20.8% Figure 3). The decrease in the lactate level positively correlated with the decrease in YMRS scores ($r=0.52$, $n=30$, $p=0.003$). There were no significant changes in NAA, myo-inositol, Cr, choline, and Glx levels between baseline and week 12 (table 2). With regard to the presence of psychotic features, no significant difference in lactate level changes following treatment with quetiapine was observed between subjects with psychotic features (n=8) and without (n=22) (18.9% vs. 23.9%, respectively, $z=-1.36$, $p=0.174$). Quetiapine dose (average dose at week 12 and mean modal dose) was not correlated with lactate change during treatment period ($r=-0.21$, $n=30$, $p=0.277$ and $r=-0.03$, $n=30$, $p=0.881$, respectively).

3.4. Tolerability

Three subjects (7.1%) reported mild daytime sedation in the first week of the trial. Two subjects (4.8%) reported occasional and transient gastrointestinal discomfort, which subsided without medical management. Three subjects (7.1%) intermittently reported mild levels of anxiety and agitation, which subsided over two to three days without other management.

4. DISCUSSION

This study was designed to examine the relationship between clinical improvement and brain metabolite changes following quetiapine treatment in patients with rapid cycling bipolar disorder.

4.1. Clinical efficacy of quetiapine treatment in patients with rapid cycling bipolar disorder

In the current study, there was a significant improvement in depressive symptoms as well as manic symptoms in the bipolar patients. This finding is partly consistent with results of previous studies that have suggested that quetiapine monotherapy is effective in reducing the depressive symptoms of bipolar patients (Calabrese et al., 2005). Since rapid cycling bipolar patients are prone to more frequent depressive episodes and more serious suicide attempts than other types of bipolar patients (Coryell et al., 2003), the observed efficacy of quetiapine on depressive

symptoms in our bipolar cohort would be a potential advantage in treating subjects with rapid cycling bipolar disorder.

As hypothesized, bipolar subjects had a significant reduction of manic symptoms after 12 weeks of quetiapine treatment with a response rate of 34.2%. This response rate was somewhat lower than that reported in clinical trials of other psychotropic medications in treating subjects with rapid cycling bipolar disorder: a 58% response rate with olanzapine treatment (olanzapine dose: 5–20 mg)(Sanger et al., 2003) and 57.6% with lamotrigine treatment (lamotrigine monotherapy and add-on dose: 141 and 273 mg/day, respectively)(Bowden et al., 1999). This potential difference may stem from several factors including differences in demographic and clinical characteristics of study subjects and the relatively low quetiapine dose used in the current study (Vieta et al., 2002). For example, the relatively low dropout rate for the 12-week study period in the present study (21%) compared to the rate for the 3-week period in the study conducted by Sanger and colleagues (2003) (26%) may have contributed to the difference in response rates.

4.2. Lactate level change following the treatment with quetiapine

In the current study, the lactate level decreased following quetiapine treatment. This finding is partly in line with a recent MRS study showing that lactate levels are increased in medication-free subjects with bipolar disorder (Dager et al., 2004). Although our study was not designed to assess lactate level differences between bipolar and comparison subjects, the substantial decrease in lactate levels following treatment with quetiapine indirectly suggests that this functional abnormality at baseline may be normalized with treatment. However, in light of the possibility that the withdrawal of mood stabilizers (about 50 percent of study subjects had prior use of lithium.) may be responsible for a short-term increase in lactate, current results should be interpreted with caution.

Further, the fact that the lactate level changes were correlated with decreases in manic symptoms and that responders showed a greater lactate level decrease than non-responders suggest that quetiapine efficacy may be related to the changes in brain lactate levels. However, since subjects in this study were all currently in manic episode, further studies will be needed to examine whether the lactate level changes following quetiapine treatment would be observed in depressive episodes of rapid cycling bipolar subjects.

Changes in cerebral lactate levels have been associated with mitochondrial dysfunction in bipolar disorder (Kato and Kato, 2000; Stork and Renshaw, 2005). Specifically, an increased level of lactate observed in bipolar subjects suggests an impaired oxidative phosphorylation in mitochondria and consequently, a shift toward glycolytic energy production (Kato and Kato, 2000; Stork and Renshaw, 2005). The fact that atypical antipsychotics including quetiapine have negligible inhibitory effects of mitochondrial oxidative phosphorylation provides a potential benefit on mitochondrial respiration when compared to typical antipsychotics (Modica-Nalolitano et al., 2003). This suggests that a decrease in lactate levels following quetiapine treatment may be related to the recovery of cellular pathology in subjects with bipolar disorder.

Given that the use of higher field MRI scanner is recommended for assessing low signal metabolites including lactate (Friedman et al., 2004), the use of a 3T scanner in the present study may add to the validity of our finding regarding lactate level changes.

Although there has been one study which reported an indirect and potential link between quetiapine treatment and NAA level change (Atmaca et al., 2007), we have not observed this relationship in the current study. Additionally, in other MRS studies of lithium-treated bipolar patients (Moore et al., 2000; Friedman et al., 2004), NAA changes (Moore et al., 2000) and

Glx changes (Friedman et al., 2004), not lactate changes, were identified. The discrepancy in findings between the current and prior reports may arise from several factors including differences in medications (quetiapine vs. lithium), severity of manic symptoms (mean score of YMRS 32.9 vs. 4.7), clinical characteristics (rapid cycling bipolar disorder vs. bipolar disorder) and the study design.

4.3. Side effects

A few bipolar patients reported mild side effects during the study period. These included sedation, gastrointestinal discomfort, anxiety and agitation. Previous studies have also demonstrated that quetiapine is well tolerated in bipolar subjects (Calabrese et al., 2005; Yatham et al., 2004; Vieta et al., 2005; Sachs et al., 2004). Due to low affinity and the rapid dissociation from the D2 receptor, quetiapine has not been associated with the prolactin elevation and extrapyramidal symptoms which have been observed with some atypical antipsychotics (Zarate, 2000; Garver, 2000).

4.4. Study limitations

There are several important limitations that should be considered in interpreting our findings. First, it was an open trial without active or placebo comparison groups. Consequently, it cannot be determined with confidence whether the improvement in clinical symptoms over the 12-week period is primarily due to quetiapine *per se* rather than the clinical course of illness, especially as these subjects are 'rapid cycling' bipolar patients. Second, for the same reason, it remains to be confirmed whether the lactate level change was induced by quetiapine or the epiphenomenon of the manic symptom improvement. Third, the mean quetiapine dose may be relatively low for treating manic symptoms, although there has been no reported standard dose of quetiapine for treating mania.

5. CONCLUSION

In summary, we have shown that antimanic efficacy of quetiapine in treating rapid cycling bipolar patients may be associated with a lactate level decrease in frontal regions of the brain. Interestingly, there has also been an improvement in depressive symptoms with quetiapine treatment in this cohort. Our results suggest that quetiapine monotherapy would be a useful candidate for safe and effective antimanic and antidepressant treatment in subjects with rapid cycling bipolar disorder.

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Abbreviations

CGI-S	Clinical Global Impression-Severity scale
HDRS	17-item Hamilton Depression Rating Scale
¹H-MRS	proton magnetic resonance spectroscopy
YMRS	Young Mania Rating Scale

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Figure 1. Midfrontal voxel-of-interest

Figure 2. Reduction of YMRS scores and HDRS scores over the 12-week period in rapid cycling bipolar patients with quetiapine treatment

Footnote:

Results of repeated measures ANOVA for YMRS and HDRS [$F(12, 444)=27.7$, $p<0.001$ and $F(12, 444)=23.9$, $p<0.001$, respectively] were presented. Pattern of CGI-S changes is similar to those of YMRS and HDRS, although data are not shown in this figure.

Plot indicates observed cases means. Error bar means 95% confidence interval and box means standard errors.

Abbreviations: ANOVA, analysis of variance; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale; CGI-S, Clinical Global Impression-Severity scale

Figure 3. Midfrontal lactate level changes in rapid cycling bipolar patients with quetiapine treatment

Pane A: Comparison of lactate level changes between baseline and week 12

Pane B: Comparison of lactate level changes between non-responders and responders

Footnotes:

There were significant differences in the lactate level in the midfrontal gray matter at baseline and week 12 [$t(29)=15.4$, $p<0.001$](Pane A). Lactate level changes of responders following the quetiapine treatment were greater than that of non-responders ($z=-2.08$, $p=0.037$)(Pane B). Plot indicates observed cases means. Error bar means 95% confidence interval and box means standard errors.

Table 1
Demographic and clinical characteristics of rapid cycling bipolar patients

	bipolar patients (n=42)	
	mean (n)	SD (%)
age (years)	31.6	7.3
sex (men)	24	53.3
handedness (right)	41	97.6
psychotic features at enrollment	11	26.2
number of episodes in the last year before enrollment	6.69	2.01
number of subjects with bipolar I disorder	42	100
previous exposure to psychotropic medications		
drug-naïve	10	23.8
exposed	32	76.2
prior use of mood stabilizers		
lithium *	21	50.0
valproate *	11	26.2
carbamazepine *	10	23.8
None	10	23.8

* The numbers are not mutually exclusive.

Abbreviations: SD, standard deviation

Table 2
Metabolite concentrations (mM) of midfrontal voxel-of-interest from proton magnetic resonance spectroscopy in rapid cycling bipolar patients (n=30)

Type of metabolite	baseline		week 12		t [*]	p-value
	mean	SD	mean	SD		
Lactate	1.74	0.15	1.35	0.16	15.4	<0.001
NAA	8.60	0.59	8.79	0.59	-1.06	0.298
myo-inositol	4.56	0.93	4.51	0.58	0.28	0.783
Creatine	6.23	0.34	6.46	0.76	-1.32	0.198
Choline	2.39	0.26	2.38	0.45	0.09	0.927
Glx	16.4	1.71	16.0	1.66	0.97	0.340

* Paired t-test was conducted to compare metabolite concentrations over time.
Abbreviations: NAA, N-acetyl-aspartate; Glx, glutamate, glutamine and gamma-aminobutyric acid peak