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Quetiapine Therapy in Treatment-Refractory Schizophrenia

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Abstract

Objective: *We investigated the effects of an atypical antipsychotic agent, quetiapine, in treatment-refractory schizophrenia.*
Methods: *The subjects were 10 inpatients who were diagnosed according to the DSM-IV criteria for schizophrenia. They were termed treatment refractory. We tried to switch patients from typical antipsychotics to quetiapine. Each patient gave informed consent for the research involved in this study. The assessment of psychotic symptoms was done before and after replacement by quetiapine administration using the Brief Psychiatric Rating Scale (BPRS). Plasma homovanillic acid (pHVA) level was also assessed. Patients took a mean dose of 602.5 mg quetiapine daily for a mean period of 100.9 days.*
Results: *(i) Although the total BPRS score did not show significant changes, three out of 10 patients (30%) showed improvement by BPRS criterion. (ii) The pHVA levels did not show significant difference between blood levels before and after replacement by quetiapine administration. (iii) There was a positive correlation between the pHVA levels at baseline and total BPRS scores. (iv) pHVA changes between baseline and quetiapine steady state (ΔpHVA) were correlated positively with BPRS changes (ΔBPRS).*
Conclusions: *Quetiapine has a greater affinity for 5-hydroxytryptamine-2 receptors than dopamine D_2 receptors. Our results indicated that typical antipsychotic replacement by quetiapine might be effective for some treatment-refractory schizophrenic patients, and changes in pHVA were correlated with the therapeutic response to quetiapine (German J Psychiatry 2001;4:63-67).*

Keywords: plasma homovanillic acid (pHVA), psychotic symptoms, quetiapine, treatment-refractory schizophrenia

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Introduction

About 25% of schizophrenic patients are thought to be resistant to conventional (typical) antipsychotic therapy (Dixon et al., 1995). Although an increased dose of a typical antipsychotic can be effective for some patients, consideration should be given to switching to one of the novel (atypical) antipsychotics. At present, only clozapine, with its risks for agranulocytosis, is clearly established as a treatment for refractory illness (Kane et al., 1988). Quetiapine is an atypical antipsychotic, low potency D-2 dopamine (DA) receptor antagonist and is relatively a more potent serotonin (5-HT)-2 antagonists than typical antipsychotic drugs. Although quetiapine has been reported to be as effective as typical antipsychotics, or more effective in schizophrenic patients, and even in a subset of patients with treatment-refractory schizophrenia (Buckley, 2001; Emsley, 1999; Maeda et al., 1999), the efficacy of quetiapine in this patient population has been poorly evaluated. To examine a hypothesis that the total Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) score may de-

crease significantly after quetiapine therapy, we evaluated the efficacy of quetiapine in treatment-refractory schizophrenic patients. Plasma homovanillic acid (pHVA) level was also assessed, since various changes in pHVA are highly correlated with the therapeutic response to antipsychotics (Friedhoff and Silva, 1998).

Methods

The subjects in this study were 10 chronically medicated schizophrenic inpatients. Diagnosis was based on DSM (Diagnostic and Statistical Manual of the American Psychiatric Association)-IV (American Psychiatric Association, 1994) criteria for schizophrenia, a detailed clinical interview, and review of the prior records. Although they did not meet the standard criteria of treatment-resistance, they had previously failed to respond to at least two different classes of typical antipsychotics in appropriate doses for at least 4 weeks each. We tried to switch patients with schizophrenia from typical antipsychotics to quetiapine. They had been admitted to the Department of Neuropsychiatry, Fujii Hospital. In the patients, hepatic and renal functions were normal, and patients were excluded if they presented with any organic central nervous system disorder, significant substance abuse, and mental retardation. In addition, the detailed clinical interview revealed that none of the subjects had adhered to a low monoamine diet. The study was approved by the relevant ethics committees and was performed in accordance with the Declaration of Helsinki II. Patients who gave informed consent to the research participated in this study. Table 1 shows the demographic characteristics of the subjects.

Since the patients had been prescribed antipsychotics with various chemical structures, each antipsychotic was converted to its haloperidol equivalent using the dosage comparability table (Inagaki et al., 1998); for depot antipsychotics, the procedure adopted was based on the equivalence table for long-term therapy (Inagaki et al., 1998). The mean converted dosage of the patients is shown in Table 1.

Psychiatric ratings were done using the BPRS in the morning of the day when blood samples for HVA were drawn. The BPRS provides a standardized method of assessing 18 psychiatric symptoms using operationally defined 7-point scales. Based on previous groupings of $BPRS_{0-6}$ symptoms (Guy, 1976), the following five BPRS factors were derived: anxiety-depression (AD), anergia (AN), thought disturbance (TD), activation (AC), hostile-suspiciousness (HS). These factors were computed by summing the relevant items of the BPRS. The mean scores of five BPRS factors in the patients are shown in Table 2. Extrapyramidal symptoms (EPS) were assessed using the Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) (Inada, 1996). The DIEPSS is composed of eight individual parameters and one global assessment constructed to measure EPS, using 5-point scales, and we considered the ratings of overall severity as the EPS scores.

Blood samples for pHVA estimation were drawn on two occasions (1) prior to quetiapine, and (2) after a mean period of 100.9 days (SD = 35.4, range 42-138) treatment. Repeated pHVA measurements in the same individual appear to increase the signal/noise ratio for pHVA by reducing the intra-individual variance in pHVA concentrations (Kahn and Davis, 1998). We, however, took just one sampling, since one assessment is practical in the clinical setting. At the time of second assessment, patients had been taking a mean dose of 602.5 mg quetiapine daily (SD = 15.2, range 300-750). Blood samples were drawn from all subjects between 0600 and 0700 h. The plasma was prepared and stored at -20 centigrade until the time of analysis. The pHVA was determined with High-Performance Liquid Chromatography (HPLC) (Gironi et al., 1988).

Because of the small sample size, statistical analyses were done using nonparametric tests.

Results

Measures of Psychotic Symptoms

The mean values of the scores in the BPRS are shown in Table 2. Quetiapine treatment of treatment-refractory schizophrenic patients was associated with a numerical decrease of the BPRS total score (15% reduction). However, there was only a trend for statistical difference ($p = .0925$). When we examined the five BPRS factors individually, none of the five difference values between pre- and post-treatment scores shown in Table 2 reached a significant level after Bonferroni correction.

When a responder was defined a priori as any patient who achieved at least a 20% reduction in BPRS total score from baseline to quetiapine steady state, three out of 10 patients (30%) showed improvement.

Table 1. Demographic Characteristics of Subjects

N (W/M)	Age (yrs)	Body weight (kg)	Duration of illness (yrs)	Dose* (mg/day)	BPRS (Total)	DIEPSS (Overall)
10	38.3	69.6	16.0	15.1	48.0	0
(1/9)	(10.7)	(11.0)	(11.0)	(9.7)	(16.4)	(1.2)

Data represent the means (SD). BPRS = Brief Psychiatric Rating Scale; DIEPSS = Drug Induced Extra-Pyramidal Symptoms Scale; *haloperidol equivalent.

pHVA Measures

The mean pHVA concentration tended to decrease (8.93 [2.69] ng/mL at baseline, and 7.33 [1.53] ng/mL in quetiapine steady state).

Psychotic Symptoms and pHVA

There was a positive correlation between the pHVA levels and total BPRS scores before replacement by quetiapine (Spearman's r = 0.681, p = .0411; Fig. 1). Moreover, pHVA changes between baseline and quetiapine steady state (ΔpHVA) were correlated positively with BPRS changes (ΔBPRS; Spearman's r = 0.748, p = .0344; Fig. 2).

Adverse Drug Reactions

The mean EPS score tended to decrease (1.0 [1.2] at baseline, and 0.5 [0.5] in quetiapine steady state).

Fig. 1. Positive Correlation between total BPRS (Brief Psychiatric Rating Scale) score and pHVA (plasma homovanillic acid) level

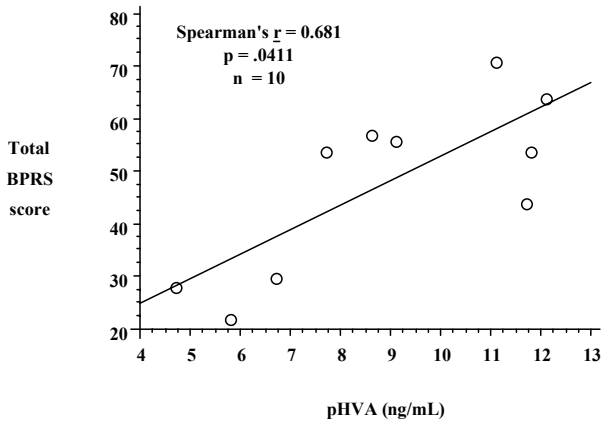
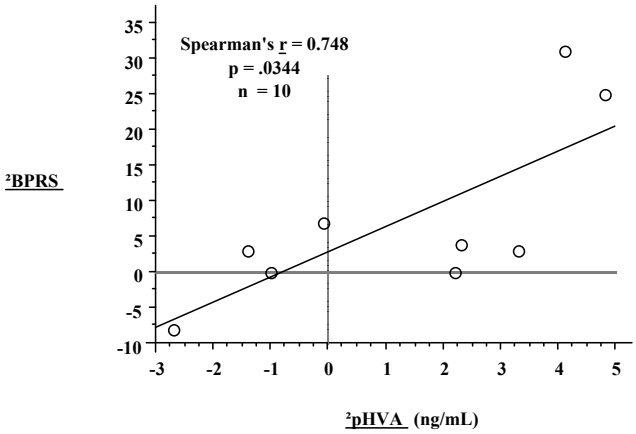


Fig. 2. Positive correlation between ΔBPRS (total BPRS score changes between baseline and quetiapine steady state) and ΔpHVA (pHVA changes between baseline and quetiapine steady state)



Discussion

Quetiapine has a greater affinity for 5-HT_2 receptors than dopamine D_2 receptors. Regarding the efficacy of quetiapine in treatment-refractory schizophrenic patients, preliminary conclusions are not possible because of a paucity of data in the literature. MEDLINE (1966-2001) search reveals one review (Hellewell, 1999) and case reports (Brooks, 2001; Szigethy et al., 1998), and a manual search revealed two studies (Emsley, 1999; Maeda et al., 1999) and a meeting abstract (Buckley, 2001). Maeda et al. (1999) reported that there was a significant improvement for treatment-refractory schizophrenic patients on quetiapine in the positive and negative syndrome scale (PANSS) (Kay et al., 1987) and BPRS total scores. Emsley et al. (1999) reported that significantly more patients on quetiapine (52%) than on haloperidol (38%) achieved a clinical response of at least 20% reduction of PANSS total score in a group of treatment-refractory schizophrenic patients, though there was a nonsignificant trend for patients on quetiapine to have greater improvement than patients on haloperidol in terms of PANSS improvement and Clinical Global Impression

Table 2. BPRS Total and Five Factor Scores

Items	Before Quetiapine Therapy	After Quetiapine Therapy	p Value	% Change
Total	48.0 (16.4)	41.0 (11.6)	0.0925	15
Anxiety-depression	10.7 (4.3)	7.5 (3.4)	0.0336	30
Anergia	10.5 (3.0)	8.8 (3.2)	0.0782	16
Thought disturbance	11.4 (5.5)	10.3 (4.6)	0.4	10
Activation	7.6 (4.4)	6.4 (2.7)	0.3	16
Hostile-suspiciousness	7.8 (3.9)	7.0 (4.5)	0.9	10

Data represent means (SD). * versus patients before replacement by quetiapine by the Wilcoxon signed rank test.

(CGI). Buckley (2001) also reported that significantly more patients on quetiapine (51%) than on haloperidol (25%) achieved a clinical response of at least 20% reduction of CGI score in a group of treatment-refractory schizophrenic patients, though there was a nonsignificant trend for patients on quetiapine to have greater improvement than patients on haloperidol in terms of PANSS or BPRS improvement.

In the present study, quetiapine treatment of treatment-resistant schizophrenic patients was associated with a numerical decrease of the BPRS total score. However, there was only a trend for statistical difference, probably due to the very small sample size. Meanwhile we found that three out of 10 patients (30%) showed improvement by BPRS criterion by switching medication from typical antipsychotics to quetiapine. Together with the previous reports, our preliminary findings indicate that typical antipsychotic replacement by quetiapine might be effective for some treatment-refractory schizophrenic patients. These results must be confirmed in large scale, double-blind studies.

It has been reported that pHVA levels are different between the groups of good responders to antipsychotics and poor responders (Chang et al., 1988; Koreen et al., 1994; Mazure et al., 1991). Mainly because of the small sample size, we could not fully analyze the data to explain the differences between responders to quetiapine and poor responders. They should also be clarified in further studies with larger sample.

In unmedicated schizophrenic patients, pHVA (Davidson et al., 1991; Davis et al., 1985; Maas et al., 1993; Pickar et al., 1984) levels have been found to be related to the severity of psychotic symptoms, though contradictory findings exist (Koreen et al., 1994; Newcomer et al., 1992). Interestingly, we found such a relation in patients with typical antipsychotic treatment, and the result is consistent with the previous reports (Davis et al., 1985; Pickar et al., 1984). Various changes in pHVA are highly correlated with the therapeutic response to typical antipsychotics (Friedhoff and Silva, 1998). A vigorous increase in initial response was predictive of a good therapeutic outcome (Davila et al., 1988) as was a later decline (Bowers et al., 1984; Pickar et al., 1984). The effects of an atypical antipsychotic clozapine on pHVA are less clear-cut than those of typical antipsychotics. For example, although clozapine tended to lower pHVA concentrations in treatment responders, the effect was small and not significant (Davidson et al., 1993). The relation between pHVA and other atypical antipsychotics in humans has been poorly evaluated. Our finding of correlation between ΔpHVA and ΔBPRS indicated that changes in pHVA might be correlated with the therapeutic response to an atypical antipsychotic quetiapine.

Conclusions

Our results indicated that typical antipsychotic replacement by quetiapine might be effective for some treatment-refractory schizophrenic patients, and changes in pHVA were correlated with the therapeutic response to quetiapine. Our results should be clarified in further studies with larger sample.

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