Prolactin Levels in Olanzapine Treatment Correlate With Positive Symptoms of Schizophrenia: Results From an Open-Label, Flexible-Dose Study

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Objective: This study was designed to investigate the relationship between the treatment effect of olanzapine and the serum prolactin level in schizophrenia and to investigate the factors that may act as predictors of response for olanzapine treatment.

Method: Sixty patients who met the DSM-IV criteria for schizophrenia were included in the study. None of the patients were drug-naive, and they were given olanzapine in a flexible dose of 10–30 mg/day for 3 months after a 7-day drug washout period. Serum prolactin levels were measured at baseline (after drug washout) and at months 1, 2, and 3 during olanzapine treatment. A psychiatrist performed monthly ratings of symptoms using the Positive and Negative Syndrome Scale Manual (PANSS Manual). The Generalized Estimating Equations-I was used for data correlation analysis. Data were gathered from July 2005 to July 2006.

Results: In general, the serum prolactin level was decreased in schizophrenia patients with olanzapine treatment, although the difference is not statistically significant ($p = .974$, $p = .246$, and $p = .363$ for the first, second, and third months, respectively). There was a close relationship between the improvement in positive symptoms and the change in serum prolactin levels before and after olanzapine treatment ($p = .002$). Moreover, the serum prolactin level also had a positive association with female gender ($p = .008$). The present study demonstrated no significant correlation between serum prolactin level, MAOA polymorphism, and DRD4 genotype.

Conclusion: This finding suggests that the serum prolactin level may be a useful biological marker to predict the effectiveness of antipsychotics in schizophrenia.

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Schizophrenia is a severe psychiatric disorder with an onset usually in early adulthood, and is frequently characterized by a chronically recurrent course. Antipsychotic drug therapy, which often must be taken throughout the person's life, remains the cornerstone of treatment for schizophrenia patients. Antipsychotic medications have been found to be the most common drugs implicated in the etiology of persistent hyperprolactinemia.[1]

Prolactin is an anterior pituitary peptide hormone that has a major role in preparing the breast for lactation and maintenance of lactation. This hormone, thus, has great physiologic importance during pregnancy and breastfeeding.[1] The synthesis and release of prolactin is inhibited by hypothalamic dopamine, which acts on D_2 receptors located on the surface of the lactotroph cells. Any process that results in a reduction in the dopamine influence of the lactotroph cell D_2 receptors would increase prolactin levels.[2] The relative risk of an elevated prolactin level needs to be considered in the treatment decision process. All antipsychotic drugs may affect serum prolactin levels to some degree. Prolactin-elevating antipsychotic drugs generally include all typical antipsychotics and risperidone. Prolactin-sparing antipsychotic drugs include clozapine, olanzapine, and quetiapine.[2,3]

The serum prolactin level may be used as an indicator of a blockade of D_2 receptors, and thus as a measure of the bioavailability of typical and atypical antipsychotics. Prolactin response to low or moderate doses of haloperidol was associated with a better clinical response, particularly with improvement of positive symptoms.[4] A similar finding was reported for risperidone.[5] Moreover, Kendler and Diehl[6] suggested that genetic factors play a role in the

etiology of schizophrenia. Monoamine oxidase (MAO) is a mitochondrial enzyme involved in the degradation of biological amines, including dopamine, serotonin, and norepinephrine.[7] Deckert et al.[8] demonstrated that the longer alleles (3a, 4, and 5) were more active than allele 3 of the MAOA gene. A recent study[7] supports the involvement of the MAOA gene with schizophrenia. On the other hand, Lung et al.[9] demonstrated that there was a significant association between the long form of the DRD4 gene and schizophrenia in Caucasians, especially those with familial schizophrenia. Based on these studies, the principal goal of our study was to test the following hypotheses: First, that the serum level of prolactin and the clinical improvement in Positive and Negative Syndrome Scale (PANSS)[10] score are related. Second, we also considered that the genetic factor would be related to the serum prolactin.

This study used a monotherapy design in a homogeneous group of patients, and applied the Generalized Estimating Equations-I (GEE-I), developed by Zeger and Liang in 1986.[11] The primary objective of this analysis was to explore the relation between clinical effects and prolactin level and to investigate the factors that may act as predictors of response for olanzapine treatment.

METHOD

Subjects

Sixty patients (36 men, 24 women) who met the diagnostic criteria for schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) were assigned to treatment with olanzapine in a 3-month study. The study was approved by the Kaohsiung Armed Forces General Hospital's Institutional Review Board, and written informed consent was obtained either from the patients or from their legal guardians after an explanation of the study was given. Data were gathered from July 2005 to July 2006.

Patients with schizophrenia who had discontinued their previous oral antipsychotics on their own for a period of at least 7 days were recruited as possible subjects at a teaching general hospital in southern Taiwan. Patients could begin this study as inpatients or outpatients, and a change in hospitalization status during participation in the study was permitted. No comorbid or other recent major Axis I disorder was allowed. Pregnant and lactating women or patients with serious medical illness in which pharmacotherapy posed a substantial clinical risk or confounded the diagnosis were excluded. Our study did not include patients with previous use of depot therapy. Pertinent demographic data are summarized in Table 1.

Table 1. Demographic and Clinical Characteristics of 60 Schizophrenia Patients Treated With Olanzapine

Variable	Value
Age, mean (SD), y	35.55 (11.53)
Age at onset, mean (SD), y	26.23 (8.40)
Duration of illness, mean (SD), y	9.32 (9.38)
Height, mean (SD), cm	64.68 (8.84)
Education, mean (SD), y	11.08 (3.68)
Sex, N	
Male	36
Female	24
Alcohol abuse, N	
No	50
Yes	10
Smoking, N	
No	37
Yes	23
Family history of schizophrenia, N	
No	43
Yes	17
MAOA polymorphism, N	
Long form	37
Short form	23
DRD4 genotype, N	
2-repeat variants	11
4-repeat variants	48
5-repeat variants	1
Preswitch antipsychotics, N	
Risperidone	12
Olanzapine	27
Clozapine	2
Quetiapine	1
Typical	18

Abbreviation: MAOA = monoamine oxidase A.

Study Design

A monotherapy (olanzapine) study design was used with a homogeneous group of patients and was started with a run-in period of 3 months. Patients were required to have discontinued using either typical or atypical antipsychotics for at least 7 days prior to the study entry.

The patients received olanzapine treatment over a period of 3 months. The dose of olanzapine was flexible, ranging from 10 to 30 mg p.o. daily, and was based on the doctor's clinical judgment. Concomitant medications were permitted throughout the trial, including anxiolytics, hypnotics, and biperiden. Serum prolactin levels were assessed at baseline (after drug washout) and at months 1, 2, and 3 during olanzapine treatment. All patients were interviewed and assessed by a senior psychiatrist who was blinded to the results of the genotype of all participants.

Assays and Clinical Evaluation

At the screen visit, a standard history, physical examination, and laboratory profile were obtained. Fasting morning blood specimens for the assays of prolactin were drawn at baseline and every month thereafter (at the end of month 1, month 2, and month 3), consecutively. The baseline data were measured immediately before starting monotherapy treatment (day 0). The samples were collected between 8 and 10 a.m. prior to medication, and serum was stored at –20°C for unit analysis. In addition, the clinical effect was evaluated by assessing the patient's symptoms at baseline (following drug washout), and

Figure 1. Mean Prolactin Level During Each Month of Study in Schizophrenia Patients With Olanzapine Treatment

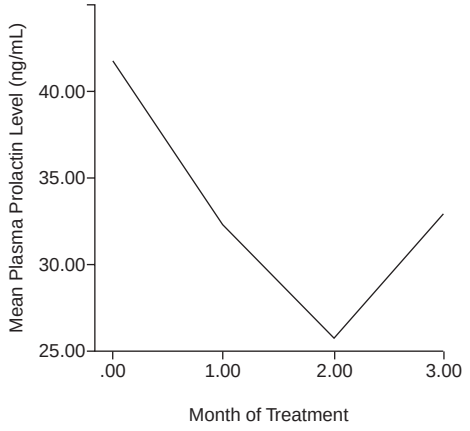

Table 2. Parsimonious Model of the Plasma Prolactin Level Change From the GEE-I (A) and GEE-I Model and Working Correlation Matrix (B) in a 3-Month Trial of Olanzapine

A.

Variable	B	95% Wald CI	p Value
Female	17.044	–29.697 to –4.390	.008
Positive symptoms of PANSS	1308.407	0.365 to 1.655	.002

B.

	Measurement[a]			
Measurement[a]	Time = 1	Time = 2	Time = 3	Time = 4
Time = 1	1.000	0.189	0.139	0.164
Time = 2	0.189	1.000	1.000	0.519
Time = 3	0.139	1.000	1.000	1.000
Time = 4	0.164	0.519	1.000	1.000

[a]Time = 1 means baseline, time = 2 means the end of 1 month, time = 3 means the end of the second month, and time = 4 means the end of the third month.
Abbreviations: GEE-I = Generalized Estimating Equation-I, PANSS = Positive and Negative Syndrome Scale.

every month thereafter for 3 months, using the PANSS. The PANSS scores can range from 30 to 210, with higher scores indicating more severe psychopathology. The PANSS includes 30 items that measure positive symptoms, negative symptoms, and general psychopathology. Supplementary items for the aggression risk profile included anger, difficulty in delaying gratification, and affective liability.

Statistical Analysis

For statistical study, SPSS 15.0 (SPSS Inc., Chicago, Ill.) was used for demographic analysis, descriptive analysis, exploratory analysis, χ^2 analysis, and the Student t test. The GEE-1 was used to analyze the independent variables of gender, age, age at onset, therapy regimen, duration of illness, family history of schizophrenia, body weight, height, compliance, educational level, polymorphism of MAOA and DRD4 genotype, family medical history, and drug and alcohol history.

RESULTS

Baseline patient characteristics for each treatment are summarized in Table 1. Thirty-seven participants (61.7%) had a long form and 23 participants (38.3%) had a short form of the MAOA polymorphism. Eleven participants (18.3%) had 2-repeat variants, 48 participants (80.0%) had 4-repeat variants, and 1 participant (1.7%) had 5-repeat variants of the DRD4 genotype. We also inquired into the use of antipsychotics by these 60 schizophrenia patients before this study. Twelve patients received risperidone, 27 were administered olanzapine, and 21 used typical antipsychotics before switching to olanzapine.

As indicated in Figure 1, olanzapine treatment was associated with a decrease in the serum prolactin level in the first 2 months, and a mild increase at the end of the third month. But in general, the prolactin level during the third month was relatively lower than the baseline level. The mean (SD) baseline serum prolactin level was 41.63 (23.09) ng/mL, the first month was 32.20 (18.02) ng/mL, the second month was 25.72 (16.77) ng/mL, and the third month was 32.86 (20.48) ng/mL. We demonstrated that there was no significantly close correlation between serum prolactin level and any of the PANSS items and the PANSS subscores (general, positive, excitement, and aggression), except the positive subscore (Table 2A). There was a close correlation between the serum prolactin level and clinical improvement in positive symptoms: the more decreased the serum prolactin level, the more improvement in positive symptoms (p = .002) (Table 2A). In the present study, we demonstrated there is a positive correlation between the serum prolactin level and the positive symptoms in female schizophrenia patients. We also found that serum prolactin has no significant association with the MAOA polymorphism and DRD4 genotype. The measurement of the GEE-1 model and the working correlation matrix in this 3-month trial of olanzapine ranged from 0.139 to 0.519 (Table 2B).

DISCUSSION

The main findings of this study were that (1) olanzapine treatment significantly decreased the serum prolactin level, (2) the prolactin level showed a more pronounced decrease in olanzapine-treated male schizophrenia patients than in female patients, and (3) there was a close relationship between the improvement in positive symptoms and the change in serum prolactin level before and after olanzapine treatment.

The results of our study suggest that olanzapine was effective in reducing the severity of overall psychotic symptoms and that olanzapine treatment significantly de-

creased prolactin levels in schizophrenia patients, which is consistent with findings from other clinical trials.[12,13] Hyperprolactinemia induced by antipsychotics occurs mainly through blockade of the D_2 receptors on the lactotrophs in the pituitary.[14] The serum prolactin level can be regarded as a signal of central dopamine function.[15] Thus, the serum prolactin level may be used as a measure of the clinical efficacy of antipsychotics. One study found a significant correlation between the serum prolactin level and haloperidol.[16]

Our data indicate that in a 3-month olanzapine treatment period, a flexible dose (ranging from 10 to 30 mg/day p.o.) causes a decrease in prolactin levels in schizophrenia patients. On the basis of the result, olanzapine seems to be superior to typical and some prolactin-elevating atypical antipsychotics in terms of this endocrinologic side effect. This finding is consistent with a previous report[17] and may be attributed to olanzapine's differential effects on dopamine neurotransmission. Kinon et al.[13] also demonstrated that mean plasma prolactin levels decreased after switching from conventional antipsychotics or risperidone to olanzapine. Our report demonstrated the same finding as this study.

Our finding indicates that female schizophrenia patients, when treated with olanzapine, show significantly more prolactin secretion than male schizophrenia patients. This is consistent with the findings of Kuruvilla and colleagues' study.[18] Kinon et al.[2] also found a similar result, with olanzapine treatment inducing greater prolactin secretion in women than in men. These results may be due to elevated prolactin values at lower reference doses in female than in male patients.[19] A recent study indicated that the pharmacokinetics and pharmacodynamics of antipsychotic drugs differ in women and men and are influenced by gender-specific factors such as body build, diet, smoking, concurrent medication, exercise, substance use, and hormonal transitions. In general, women require lower doses in order to stay well.[20]

As for measuring plasma prolactin levels and assessing the clinical effect, we used a working correlation matrix with generalized linear models for repeated measures to compare baseline and each month's data. The GEE is a very popular statistical method for analyzing longitudinal data in which correlations exist among repeated observations. One of the advantages of the GEE modeling approach is its robustness in the structure of the working correlation matrix. Thus, for moderate sample sizes, the GEE approach is a good choice.[21]

Our data indicated that the more improvement shown in the positive symptoms of these olanzapine-treated schizophrenia patients, the greater the serum decrease of the prolactin level. We should consider the interaction between the serotonergic system and prolactin secretion. Olanzapine combines stronger affinities for the serotonin ($5\text{-}HT_2$), muscarinic, and histamine receptors than dopamine D_2 receptors. The dopamine D_2 and $5\text{-}HT_2$ system have been shown to be overactive in schizophrenic patients. Serotonin is thought to be involved in schizophrenia because the hallucinogen lysergic acid diethylamide (LSD) is a 5-HT agonist. The occurrence of human cerebellar 5-HT receptors is equivocal and their status in schizophrenia unknown. It has been found that in schizophrenia, there is a reduced number of $5\text{-}HT_{2A}$ receptors and an increase in the number of $5\text{-}HT_{1A}$ receptors in the frontal cortex.[5] Zhang et al.[22] also postulated that the 5-HT system may be implicated in prolactin release. The $5\text{-}HT_{2A}$ receptor–blocking properties of atypical antipsychotics seem to reduce prolactin secretion. This issue, therefore, requires further investigation.

Kendler and Diehl[6] suggested that genetic factors play a role in the etiology of schizophrenia. A review of previous studies[7,9] revealed that the MAOA polymorphism and the DRD4 genotype have been demonstrated to be related to schizophrenia. To date, no study on the association between the serum prolactin level and the DRD4 and MAOA gene in olanzapine-treated schizophrenia patients has been published. In the present study, we found that these genetic factors have no association with the plasma prolactin level. This may be the result of olanzapine treatment.

These 60 schizophrenia patients were not new cases and had received typical or atypical antipsychotics for a period of time. An inquiry was made into the prestudy antipsychotics that were administered. We analyzed the association between the serum prolactin level in schizophrenia and the kind of prestudy antipsychotics used. The results showed that there was no association between the serum prolactin level and the prestudy typical or atypical antipsychotics. Possibly, this result occurred because there were many kinds of typical antipsychotics used and several complicated situations were not taken into account. A larger sample size and more refined study design would be needed to perfect the study.

There are several limitations to our study: (1) a small number of patients were enrolled, (2) the duration of the clinical trial was not long enough, (3) due to the safety concerns of the patients, the washout period was not long enough, and (4) monotherapy with olanzapine was used without a comparison drug.

In conclusion, some of our findings are not fully consistent with previous studies. It is important to consider factors that may be responsible for these differences. When evaluating the serum prolactin level change in these olanzapine-treated patients, it is important to understand that the baseline levels of prolactin may have been affected by various prestudy antipsychotics. This study in chronic schizophrenia demonstrated that there was a close relationship between the improvement in positive symptoms in female patients and the change in the serum prolactin level before and after olanzapine treatment. We

suggest that the results of the present study can contribute to the use of the serum prolactin level as a biological marker to predict the therapeutic effect of schizophrenia treatment. Because the level of serum prolactin tended to decrease the more positive symptoms improved, drug-induced prolactin secretion should be considered when treating schizophrenia patients with antipsychotics, and prolactin-elevating drugs should be avoided. Recognizing antipsychotic drugs with a favorable prolactin profile would be important in alleviating the morbidities associated with drug-induced prolactin elevation.

Drug names: biperiden (Akineton), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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