Effects of Olanzapine on Prolactin Levels of Female Patients With Schizophrenia Treated With Risperidone

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Background: This study was conducted to prospectively examine the effect of switching from risperidone to olanzapine on female schizophrenia patients who experienced menstrual disturbances, galactorrhea, and/or sexual dysfunction.

Method: Twenty female patients with DSM-IV schizophrenia who were taking risperidone and were suffering from menstrual disturbances, galactorrhea, and/or sexual dysfunction were enrolled. Patients were switched from risperidone to olanzapine over a 2-week period, then treated with olanzapine for 8 additional weeks. The serum prolactin concentrations were examined every 2 weeks. The Positive and Negative Syndrome Scale (PANSS), Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale for Extrapyramidal Symptoms (SAS), and questions from the Dickson-Glazer Sexual Functioning Scale were administered to evaluate efficacy, extrapyramidal side effects, and sexual and reproductive functioning at baseline and the endpoint of 10 weeks.

Results: Serum prolactin levels decreased significantly ($p < .01$) following the switch from risperidone to olanzapine. Scores of PANSS, AIMS, and SAS at the endpoint were also significantly decreased ($p < .01$) compared to those of baseline. Patients experienced improvements in menstrual functioning and perceptions of sexual side effects.

Conclusion: Olanzapine reversed hyperprolactinemia in risperidone-treated female schizophrenic patients. This was associated with a decrease in amenorrhea, improved cycle regularity, and a decrease in sexual side effects that the women attributed to antipsychotic medication. This study suggests that switching to olanzapine is a safe and effective alternative method for patients with antipsychotic-induced hyperprolactinemia associated sexual and/or reproductive dysfunction. Long-term follow-up studies are warranted, with particular attention to the course of sexual and reproductive dysfunction.

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Antipsychotic drugs are the treatment of choice for patients with schizophrenia, but side effects can make these drugs difficult to tolerate, adversely impacting drug compliance and, therefore, treatment outcome.[1,2] Antipsychotic medications can cause sexual and reproductive side effects.[3–7] Better understanding of these side effects and management strategies may contribute to improved care for individuals who often must take these drugs lifelong to control their illnesses.

Elevated serum prolactin levels are often cited as a cause of sexual and reproductive side effects in neuroleptic-treated patients, but the pathomechanisms of reproductive and sexual dysfunction in psychiatrically ill patients are complex.[4,8,9] Drug-induced sexual side effects may be (1) an indirect consequence of the antipsychotic, for example, sedation secondary to the effects on the central nervous system; (2) a direct effect by affecting neurotransmission in the central and the peripheral nervous system; and (3) a result of effects on the neuroendocrine system impacting gonadal steroids and prolactin.[10] In female patients, not only sexual dysfunction, but also galactorrhea, breast tenderness, and menstrual disturbances have been attributed to neuroleptic-induced hyperprolactinemia (NIHP) caused by unwanted blockade of dopamine D_2 receptors of the tubero-infundibular tract.[4,11,12]

Unlike traditional neuroleptics and risperidone, some of the novel antipsychotic drugs—clozapine,[13] olanzapine,[14] and quetiapine[15]—have no or minimal propensity to increase serum prolactin.[7,16,17] Thus, as there are efficacious

prolactin-sparing antipsychotics available, it is now possible to begin to study whether there are in fact differences in the frequency and severity of sexual and reproductive side effects related to changes in prolactin levels.

Postmarketing case reports suggest that risperidone can induce significant serum prolactin increases associated with sexual dysfunction, galactorrhea, and menstrual dysfunction that may be reversed by switching to typical neuroleptics that cause less prolactin elevation or to olanzapine or clozapine.[4,7,17,18–26] However, there is a lack of systematic data, especially in women with schizophrenia, of the impact of individual antipsychotic medications on menstruation and sexual functioning.

This study was conducted to prospectively examine the effect of olanzapine on female patients with schizophrenia suffering from menstrual disturbances, galactorrhea, and/or sexual dysfunction while on risperidone treatment in terms of prolactin levels, sexual function, psychopathology, and extrapyramidal side effects.

METHOD

Subjects

Female patients between the ages of 18 and 45 years who were of childbearing potential and who were diagnosed as having schizophrenia (DSM-IV)[27] were consecutively recruited from both inpatient and outpatient units of the Department of Psychiatry, St. Mary's Hospital, Seoul, Korea. Inclusion criteria were (1) treatment with risperidone as an exclusive antipsychotic drug for at least 4 weeks and (2) presence of sexual and/or reproductive side effects, that is, at least 1 of the following: reduction of libido, dissatisfaction with sexual functioning, disturbance in vaginal lubrication during intercourse, anorgasmia, galactorrhea, amenorrhea, or change in the regularity of the menstrual cycle and/or amount of bleeding, identified in the clinical setting by the authors (W.-M.B, T.-Y.J, D.-J.K). Women who had recently been taking oral contraceptives or had a history of hysterectomy or oophorectomy were excluded, as were pregnant or lactating women and patients with serious medical illnesses. Of 30 eligible patients, 25 subjects signed a written informed consent form approved by the local Institutional Review Board and were enrolled for this study. Twenty subjects completed the trial, and 5 patients were dropped because of noncompliance to medication and/or clinic visits.

Administration of Olanzapine

Continuation of risperidone treatment was allowed during the first 2 weeks of switching to olanzapine, then olanzapine was given exclusively for 8 weeks. Olanzapine treatment was initiated at 5 mg daily and was titrated to a maximum of 20 mg daily at the discretion of the attending psychiatrist.

Measurement of Prolactin Concentration

Five mL of blood was collected at a consistent time of day (8:00–9:00 a.m. to minimize the potential confounding effects of circadian rhythms on prolactin secretion) at baseline and at 2, 4, 6, and 8 weeks after starting olanzapine monotherapy. The serum was collected by centrifugation of the blood, frozen and stored at –20ºC. The serum prolactin concentration was measured by standard radioimmunoassay.

Efficacy and Safety Evaluations

The Positive and Negative Syndrome Scale (PANSS)[28] was administered at baseline before starting olanzapine and at the endpoint of 10 weeks. Questions from the Dickson Glazer Sexual Functioning Scale (DGSFS),[17,29] a computerized self-assessment instrument for use in antipsychotic-treated patients, currently in development, were translated into Korean and adapted by the authors for administration by pen and paper. To evaluate the impact on sexual and reproductive functioning of the drugs, this instrument was administered on 5 occasions at the same time that prolactin levels were drawn. Descriptive data collected included marital status; whether patients had ever had sex with a partner and if so, if they were in a current sexual relationship; whether they were taking birth control pills; whether they had had a hysterectomy; menopausal status; and number of pregnancies and births. Questions on perceptions of sexual side effects included (1) the patients' rating of how bothered they were by sexual side effects on a 5-point scale ranging from "not bothered at all" to "extremely bothered" and (2) one question each on the patients' beliefs of the impact of the drug (risperidone at baseline and olanzapine at other timepoints) on frequency of sexual thoughts, vaginal lubrication, ability to have an orgasm, and overall satisfaction with sex. The latter questions allowed for increase, decrease, or no change attributed to the drug. In addition, the patients were asked about galactorrhea during the preceding 2 weeks, and if present, how severe it was on a 5-point scale ranging from present only with nipple stimulation to almost continuous occurring during the day and night. Menstrual cycles were assessed by asking (1) when the last menstrual period occurred, within the past 1, 2, or 6 months, 1 year, or longer than 1 year; and (2) whether periods had been regular, irregular, or absent over the prior 3 months.

Extrapyramidal side effects were evaluated using the Abnormal Involuntary Movement Scale (AIMS)[30] and the Simpson-Angus Scale for Extrapyramidal Symptoms (SAS)[31] at the baseline and endpoint.

Data Analysis

All the data collected in the study were analyzed using SPSS for Windows version 9.0 (SPSS, Inc., Chicago, Ill.). p Values less than .05 were considered as significant.

Table 1. Data on Psychopathology and Safety Measures in Subjects With Schizophrenia Before and After Treatment of Olanzapine (Student paired t test)[a]

Rating Scale Score	Baseline	8 Weeks	t	p Value
PANSS				
Total	60.2 ± 12.1	51.2 ± 14.7	4.1	< .01
Positive symptom scale	14.3 ± 4.8	11.4 ± 4.8	3.9	< .01
Negative symptom scale	15.9 ± 3.2	13.8 ± 3.7	3.3	< .01
General symptom scale	31.0 ± 5.3	26.0 ± 7.4	3.8	< .01
AIMS	1.7 ± 1.0	1.0 ± 0.8	4.5	< .01
SAS	1.3 ± 1.1	1.0 ± 0.8	3.0	< .01

[a]Abbreviations: AIMS = Abnormal Involuntary Movement Scale, PANSS = Positive and Negative Syndrome Scale, SAS = Simpson-Angus Scale for Extrapyramidal Symptoms. Rating scale scores shown as mean ± SD.

Table 2. Menstrual Function at Baseline and Endpoint

	Baseline (risperidone; N = 20)		Endpoint (olanzapine; N = 20)	
Variable	N	%	N	%
Last menstrual period				
Within past month	6	30	11	55
Within past 2 months	3	15	3	15
Menstrual cycles				
Absent	12	60	5	25
Irregular	8	40	11	55
Regular	0	0	4	20

PANSS, AIMS, and SAS scores were also analyzed by comparing the data at baseline and endpoint using the paired t test. The changes in the individual questions of the DGSFS at baseline and endpoint were analyzed using the Wilcoxon signed rank test. The changes in the serum prolactin concentration measured at baseline and 2, 4, 6, and 8 weeks after the exclusive treatment of olanzapine were analyzed using a repeated-measure analysis of variance, and a Bonferroni test was done for comparison of each period. The correlation of the serum prolactin concentration and the individual questions of the DGSFS at baseline and endpoint was analyzed using the Spearman nonparametric correlation test. Descriptive data from the DGSFS were reported for the entire cohort; there were no differences between baseline and endpoint.

RESULTS

Demographics

The mean ± SD age of patients was 34.4 ± 6.1 years, age at first onset was 26.6 ± 8.7 years, duration of illness was 6.8 ± 5.3 years, and total duration of treatment was 5.5 ± 4.2 years. The mean duration of risperidone treatment was 7.9 ± 7.0 weeks (range, 4–25 weeks). The mean daily dosage of risperidone at baseline was 3.5 ± 1.2 mg, and the mean daily dosage of olanzapine during the 8 weeks post-switch was 9.1 ± 1.8 mg.

Changes in Serum Prolactin Concentration After Olanzapine Treatment

The mean serum prolactin concentration at the baseline was 132.2 ± 59.1 ng/mL. The serum prolactin concentration significantly decreased to 25.6 ± 22.3 ng/mL after 2 weeks of olanzapine treatment, 26.3 ± 26.6 ng/mL after 4 weeks, 22.0 ± 24.8 ng/mL after 6 weeks, and 23.4 ± 22.7 ng/mL after 8 weeks ($F = 112.8$, $p < .01$).

The Bonferroni test showed that the level of serum prolactin between baseline and the second week ($p < .01$), fourth week ($p < .01$), sixth week ($p < .01$), and eighth week ($p < .01$) were all significantly different. There was no significant change in the prolactin level between the second and the fourth week, the fourth and the sixth week, and the sixth and the eighth week.

Changes in Clinical Symptoms After Olanzapine Treatment

Comparing the scores on the PANSS at the baseline and those at the eighth week after olanzapine initiation, scores on all 3 symptom subscales were significantly decreased (Table 1).

Evaluation of Safety After Olanzapine Treatment

Comparing the scores on the AIMS and SAS at baseline and the endpoint, both were significantly decreased (see Table 1).

Sexual Function, Menstruation, and Galactorrhea

Seven (35%) of 20 subjects were never married, while the remainder were married (N = 10; 50%) or divorced (N = 3; 15%). Of the 13 women reporting past pregnancies, 1 had not given birth, 5 reported 1 childbirth, 5 had 2 childbirths, and 2 had 3 childbirths. Most women (N = 19; 95%) indicated that they are heterosexual, but 1 (5%) responded "don't know." Six subjects (30%) had never had sex with a partner, and 14 (70%) reported that they had. Eight (40%) reported that they were in a current sexual relationship, while 12 (60%) said they were not.

At baseline on treatment with risperidone, 25% (N = 5) of the women reported galactorrhea within the past 2 weeks, while by 8 weeks of olanzapine treatment 20% (N = 4) reported persistent galactorrhea. Except for 1 patient at endpoint who reported that spontaneous secretion of a few drops of milk occurred, the remainder reported milk leakage only with nipple stimulation.

Most changes in individual questions adapted from the DGSFS were not statistically significant, but all changes were in the direction of improved functioning. The number of women reporting regular or irregular periods versus absent cycles significantly increased by the end of the study ($z = 2.81$, $p = .005$). The number of women with a last menstrual period within the past 1 or 2 months also increased, but this did not reach statistical significance ($z = 1.66$, $p = .097$) (Table 2).

Table 3. Perceived Effects of Antipsychotic Medication on Sexual Functioning in Subjects With Schizophrenia at Baseline and Endpoint (N = 20)

	Baseline (risperidone)		Endpoint (olanzapine)	
Variable	N	%	N	%
Frequency of sexual thoughts				
Fewer	9	45	7	35
No effect	11	55	11	55
More	0	0	2	10
Amount of vaginal lubrication				
Decreased	10	50	4	20
No effect	10	50	14	70
Increased	0	0	2	10
Ability to have orgasm				
Decreased	8	40	4	20
No effect	12	60	14	70
Increased	0	0	2	10
Satisfaction with sex				
Decreased	9	45	4	20
No effect	10	50	14	70
Increased	1	5	2	10

In regard to the women's perceptions that the antipsychotic medications caused sexual side effects, 50% of women (N = 10) at baseline on risperidone treatment were not bothered by sexual side effects, while by endpoint on olanzapine treatment this frequency increased to 70% (N = 14). See Table 3 for perceived medication effects on frequency of sexual thoughts, vaginal lubrication, effects on orgasm, and satisfaction with sex. At baseline, the serum prolactin concentration was significantly correlated with the number of months for amenorrhea ($r = 0.49$, $p = .027$). Other measures of sexual and/or reproductive dysfunction by the DGSFS were not correlated with the level of serum prolactin.

DISCUSSION

To our knowledge, this is the first prospective report of changes in serum prolactin levels and sexual and reproductive functioning after switching from risperidone to olanzapine in female patients with schizophrenia suffering from menstrual and/or sexual dysfunction. In addition, concurrent prospective measurements of psychopathology and movement disorders were completed.

Our findings are consistent with prior case reports of (1) risperidone markedly increasing prolactin levels in premenopausal women and (2) olanzapine causing minimal changes in serum prolactin.[14,32–36] It also supports the finding of the double-blind study of olanzapine and risperidone[37] that hyperprolactinemia was significantly less in olanzapine-treated patients.

Of note, elevations of prolactin during risperidone treatment occurred at relatively low doses (mean = 3.5 ± 1.2 mg). The prolactin levels at 2 and 8 weeks were 81.1% and 82.5% decreased from baseline, respectively. At endpoint, 16 women (80%) had levels within normal limits (< 20 ng/mL), and 4 women continued to have mildly elevated levels (< 2-fold elevation of the upper limit of normal).

The 10-week period of this study is a short time to study menstrual cycles since amenorrhea is defined as the length of time equivalent to a total of at least 3 of the previous cycle intervals or 6 months of absent periods,[38] but changes were noted in the direction expected given the decrease in prolactin levels following the medication switch. The small sample size limits the power of this study. The number of women reporting periods within the past 2 months prior to testing increased from 9 (45%) at baseline to 14 (70%) at endpoint. The percentage of women reporting absent menses decreased from 60% (N = 12) at baseline to 25% (N = 5) at the end of 10 weeks, 8 weeks of olanzapine monotherapy. This finding is consistent with prior case reports of risperidone-associated amenorrhea[18] and with improvement of menstrual functioning with switching to olanzapine.[17,24,25]

Fewer women reported being bothered by sexual side effects and attributed less impairment of frequency of sexual thoughts, vaginal lubrication, ability to experience orgasm, and sexual satisfaction to olanzapine than to risperidone treatment. These results suggest that olanzapine may cause fewer sexual and reproductive side effects than risperidone, but clearly given (1) the variable length of risperidone treatment prior to switching to olanzapine, (2) the lack of pre-illness menstrual and sexual histories, and (3) the chronic nature of the illnesses, all of the baseline abnormalities cannot be attributed to risperidone. While these improvements occurred concurrent with decreasing prolactin levels, it is possible that other pharmacologic differences between risperidone and olanzapine may have contributed. Whether the decrease in psychopathology and movement disorders contributed to the women's reported improvement in sexual and reproductive functioning is unclear. In addition, the sample was small, and the DGSFS from which the questions were translated is still in development and requires further psychometric validation.

It is interesting that despite high prolactin levels on risperidone treatment, only 25% of patients reported galactorrhea at baseline, and despite reduction in prolactin levels, 20% of these women continued to experience milk secretion. Whether more women would have developed galactorrhea with a longer duration of persistent prolactin elevations is possible, as 16 patients were on risperidone treatment for 8 weeks or less. However, not all women with hyperprolactinemia display galactorrhea. The absence may be due to an accompanying hypoestrogenic state in women with hyperprolactinemia.[38] In addition, galactorrhea on treatment with phenothiazines can persist for 3 to 6 months after drug treatment is discontinued,[38] so the study may have been too short to expect resolution of this side effect.

Although all 3 components of PANSS—positive symptoms, negative symptoms, and general symptoms—were

significantly decreased following the switch to olanzapine, and there were favorable changes in AIMS (35.3% decline) and SAS (30.8% decline) scores at endpoint compared with baseline, it is not possible to conclude that olanzapine in general has better efficacy on psychotic symptoms and a safer side effect profile than does risperidone. A more comprehensive inventory of outcome variables and a longer trial would have to be designed to validate this early impression of olanzapine's relative risk-benefit value compared with risperidone in premenopausal women. However, considering these results together with the positive trends in resolution of sexual and reproductive side effects, it is possible to conclude that the switch from risperidone to olanzapine in female patients with schizophrenia who are experiencing symptomatic hyperprolactinemia is effective and safe.

Many factors influence prolactin secretion, such as diurnal rhythms, exercise, sexual activity, menstrual cycles, stress, and duration and type of neuroleptic treatment.[6,39–41] The results, as expected, showed high variability in severity of elevation of serum prolactin concentration. This may be due in part to individual differences in sensitivity of the hypothalamic-pituitary axis to dopamine blockade and differences in prior antipsychotic treatment regimen. Since it had been suggested that there is a correlation of serum prolactin increases with increased dosage of antipsychotic drugs,[6] a future study of fixed-dose design would be helpful to delineate the effects of newer antipsychotics on serum prolactin. Despite limitations of this study, our results clearly demonstrate that hyperprolactinemia associated with risperidone treatment is reduced by switching to olanzapine. Prior to the introduction of prolactin-sparing antipsychotics, interventions for sexual and reproductive side effects secondary to NIHP were limited to dosage reduction or discontinuation of the antipsychotic, or treatment with a dopamine agonist.[1,2] As demonstrated in this study, an additional option for patients who suffer from complications of NIHP is to switch to a prolactin-sparing atypical antipsychotic that does not carry the risk of exacerbation of psychosis that these earlier options did.

In summary, although further controlled studies with larger samples of both male and female patient groups and longer-term follow-up is desirable, the present study suggests that switching to olanzapine is a reasonable treatment option for subjects with NIHP with sexual and/or reproductive dysfunction.

Drug names: clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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