Risperidone Added to Clozapine: Impact on Serum Prolactin Levels

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Background: Several years ago, we reported that the addition of risperidone to clozapine improved response in some patients with schizophrenia. Risperidone, in general, is well tolerated when administered as monotherapy, but has been linked to a persistent elevation of serum prolactin and associated symptoms. The goal of this study was to determine whether the addition of risperidone to clozapine results in an elevation of serum prolactin levels in patients with chronic schizophrenia or schizoaffective disorder.

Method: Twenty patients on clozapine-risperidone combination therapy were matched for age and gender with 20 patients treated with clozapine monotherapy. Demographic information was gathered along with clozapine and risperidone dose and the length of time on risperidone. Serum prolactin levels were measured from a single blood sample.

Results: The 2 groups did not differ in age, race, gender, diagnosis, age at clozapine initiation, age at onset, Abnormal Involuntary Movement Scale scores, or clozapine dose. The mean ± SD serum prolactin level was 8.42 ± 4.17 ng/mL for clozapine monotherapy patients and 35.76 ± 17.43 ng/mL for combination therapy patients. The 2 medication categories showed a significant difference in log prolactin values ($t = -7.97$, $df = 38$, $p \leq .0001$). Sixteen combination therapy patients (80%) exhibited elevated prolactin levels (range for entire group, 9.7–69.8 ng/mL) while only 2 clozapine monotherapy patients (10%) exhibited prolactin elevation levels (range for entire group, 2.4–20.2 ng/mL; $df = 1$, $p < .0001$).

Conclusion: The combination of risperidone and clozapine appears to result in a moderate elevation of serum prolactin levels. Additionally, controlled prospective studies are needed to clarify the risks of long-term elevations of serum prolactin level.

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Clozapine, an atypical antipsychotic agent, remains the most effective agent for the treatment-resistant schizophrenia population. Some clozapine patients, although able to remain out of the hospital, continue to have significant symptoms despite adequate doses of clozapine. In other symptomatic patients, the clozapine dose is limited by significant side effects. Several years ago, we reported that the addition of another atypical antipsychotic agent, risperidone, to clozapine improved response in some of these patients.[1] In that open trial, we found significant improvements in ratings of positive, negative, and depressive symptoms. After the study, continued augmentation with risperidone allowed us to reduce clozapine doses and associated side effects. Recently, Raskin et al.[2] reported 3 cases of refractory schizophrenia that responded to the combination of clozapine and risperidone with a reduction in positive and negative symptoms. There have been several other reports in which this clinical intervention was effective.[3–7]

The addition of risperidone to clozapine was well tolerated in the 12 patients in our open trial and did not affect clozapine serum levels, but we did not measure prolactin levels. Risperidone, in general, is well tolerated when administered as monotherapy, but has been linked to a persistent elevation of serum prolactin and associated symptoms.[8–14] Elevation of prolactin with risperidone is common and may be greater than with conventional agents, but the frequency of clinical manifestation may be as low as 10%, and the relationship of symptoms to serum concentrations is unclear.[13]

It is not known whether the combination of risperidone and clozapine also results in a persistent elevation of serum prolactin. It has been suggested that serotonin-2 ($5\text{-}HT_2$)

Table 1. Demographic Data, Weight, and Serum Prolactin Level Results Comparing Patients Treated With Clozapine Monotherapy and Clozapine and Risperidone Combination in Patients With Chronic Schizophrenia[a]

Variable	Clozapine Monotherapy (N = 20)	Clozapine/Risperidone Combination (N = 20)
Men, N	18	18
Women, N	2	2
Age, y	43.55 ± 9.18	45.65 ± 8.98
Age at onset, y	20.15 ± 3.50	21.75 ± 4.14
Age began clozapine, y	40.47 ± 7.69	41.89 ± 7.02
Weight, lb (kg)	191.98 ± 34.12 (86.4 ± 15.4)	217.20 ± 37.75 (97.7 ± 17.0)*
BMI (kg/m^2)	29.14 ± 5.50	33.07 ± 5.34*
Length of time taking risperidone, mo	...	44.45 ± 20.41
Clozapine dose, mg/d	395 ± 98.88	445 ± 136.35
Risperidone dose, mg/d	...	6.20 ± 2.48
Prolactin level, ng/mL	8.42 ± 4.17	35.76 ± 17.43**

[a]All values presented as the mean ± SD unless otherwise indicated.
*p < .05.
**p < .001.

blockade by clozapine is protective against prolactin elevation, but this does not seem to be true for risperidone, which also provides high levels of 5-HT$_2$ blockade.[15] If prolactin elevation is primarily determined by dopamine D$_2$ receptor occupancy, the addition of risperidone to clozapine would be expected to result in elevated prolactin levels. Alternatively, if clozapine acts on other neurotransmitter systems to protect against hyperprolactinemia, risperidone augmentation would not be expected to raise serum prolactin levels.

The goal of this study was to determine whether the addition of risperidone to clozapine results in an elevation of serum prolactin levels in chronic schizophrenia and schizoaffective disorder patients.

METHOD

This study was conducted in the outpatient clinic of an urban mental health center. Records of 110 patients receiving treatment with clozapine were reviewed. Twenty patients were identified as receiving treatment with a combination of clozapine and risperidone. All 20 patients treated with the combination of clozapine and risperidone agreed to participate in this study. The 20 patients on combination therapy were matched for age and gender with 20 patients treated with clozapine monotherapy. Demographic information was gathered for age, gender, body mass index (BMI), age at onset, diagnosis, age at clozapine initiation, history of Abnormal Involuntary Movement Scale (AIMS) scores, clozapine and risperidone dose, the length of time on risperidone treatment, and the use of selective serotonin reuptake inhibitors (SSRI). Subjects were excluded if they were currently receiving treatment with levodopa, bromocriptine, thyroid hormones, or estrogen or testosterone replacement. Subjects were required to have normal thyroid-stimulating hormone levels within 6 months of the study. None of the subjects had a history of pituitary abnormalities or other hormone abnormalities. Serum prolactin levels were measured from a single blood sample drawn in the morning between 9 and 11 a.m. The normal range for serum prolactin is 0 to 15 ng/mL in men and 0 to 20 ng/mL in women.

Statistical Methods

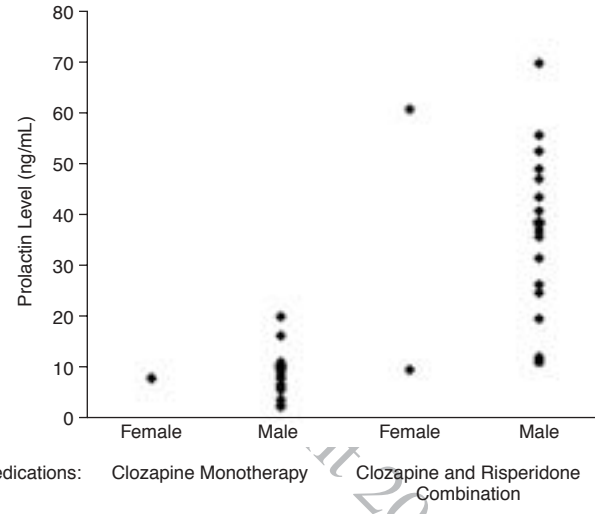
The 2 medication groups (monotherapy and combination therapy) were compared on categorical variables by Fisher exact test and on continuous variables by t test. Log prolactin was compared between groups by t test. Log prolactin was also compared between groups by analysis of covariance (ANCOVA) controlling for BMI because of an imbalance in BMI between groups. In the combination therapy group, linear regression was used to model the dependence of log prolactin on clozapine dose, duration of risperidone treatment, risperidone dose, BMI, age at onset, and age at start of clozapine treatment. In the monotherapy group, linear regression was used to model the dependence of log prolactin on clozapine dose, BMI, age at onset, and age at start of clozapine treatment. The percentage of patients with elevated serum prolactin levels was compared between groups by Fisher exact test. Two-sided p values less than or equal to .05 were considered significant.

RESULTS

Of 110 patients treated with clozapine, 20 (18.18%) were receiving combination treatment. Forty patients were recruited and agreed to participate in the study: 20 receiving clozapine monotherapy (18 men [90%] and 2 women [10%]) and 20 receiving combination therapy (18 men and 2 women). Nineteen patients (95%) on clozapine monotherapy were white, and 1 was Hispanic (5%); 17 patients (85%) on combination therapy were white, and 3 (15%) were African American. Twelve monotherapy patients (60%) were diagnosed with chronic schizophrenia and 8 (40%) with schizoaffective disorder, while 14 patients (70%) in the combination therapy group were diagnosed with chronic schizophrenia and 6 (30%), with schizoaffective disorder. Fourteen patients (70%) were treated with risperidone because of positive symptoms, 2 (10%) for negative symptoms, and 4 (20%) in order to reduce clozapine dose and side effects.

The 2 groups did not differ in age, race, gender, diagnosis, age at clozapine initiation, age at onset, AIMS scores, or clozapine dose (Table 1). The mean weight was 191.98 ± 34.12 lb (86.4 ± 15.4 kg) for clozapine monotherapy patients and 217.20 ± 37.75 lb (97.7 ± 17.0 kg)

Figure 1. Serum Prolactin Levels (ng/mL) of Clozapine Monotherapy Patients and Clozapine-Risperidone Combination Patients With Chronic Schizophrenia



for combination therapy patients, and the BMI was 29.14 ± 5.50 kg/m^2 and 33.07 ± 5.34 kg/m^2 for clozapine monotherapy patients and combination therapy patients, respectively. A significant difference in weight ($t = -2.26$, $df = 38$, $p = .0296$) and BMI ($t = -2.30$, $df = 38$, $p = .0273$) was found between the 2 groups. Nine (45%) of 20 monotherapy patients were also treated with SSRIs (3 fluoxetine, 3 sertraline, and 3 paroxetine) compared with 10 (50%) of 20 combination therapy patients (3 fluoxetine, 4 sertraline, and 3 paroxetine).

The mean serum prolactin level was 8.42 ± 4.17 ng/mL for clozapine monotherapy patients and 35.76 ± 17.43 ng/mL for combination therapy patients (Figure 1). The 2 medication categories showed a significant difference in log prolactin values ($t = -7.97$, $df = 38$, $p \leq .0001$). Sixteen combination therapy patients (80%) exhibited elevated serum prolactin levels (range for entire group, 9.7–69.8 ng/mL), whereas only 2 clozapine monotherapy patients (10%) exhibited prolactin elevation (range for entire group, 2.4–20.2 ng/mL; $df = 1$, $p \leq .0001$). The group difference in log prolactin remained significantly increased in an ANCOVA model controlling for BMI ($t = -7.34$, $df = 37$, $SE = 0.0917$, $p = .0001$); however, the effect of BMI was not significant ($p = .9235$).

Within the combination therapy group only, in a multivariate model including age, age at onset, age at clozapine initiation, clozapine dose, length of time on clozapine treatment, and BMI, only risperidone dose significantly affected log prolactin values (slope = 0.18; $t = 2.30$, $df = 10$, $SE = 0.078$, $p = .0440$). The mean risperidone dose for combination therapy patients was 6.20 ± 2.48 mg/day. The mean time on risperidone treatment was 44.45 ± 20.41 months for combination therapy patients. For the clozapine monotherapy group, age, clozapine dose, BMI, age at onset, and age at clozapine initiation did not significantly affect log prolactin values.

DISCUSSION

Combination therapy with 2 or more antipsychotic agents is becoming common in general clinical practice, but with little understanding of the metabolic and endocrinologic effects. However, the combination of risperidone and clozapine appears to result in elevations of serum prolactin levels. The long-term impact of elevated serum prolactin remains uncertain in the schizophrenic population. Sexual dysfunction is one possible outcome, but whether the elevated serum prolactin results in a reduction in bone density in men with schizophrenia is poorly understood. In the general population, elevation of serum prolactin levels, particularly in women, may result in a decrease in bone density and an increased risk of bone fractures.[16,17] There are no reports of increased risk of bone fractures in patients with schizophrenia despite evidence that conventional agents and risperidone persistently elevate serum prolactin levels.

This study has major limitations. The cross-sectional design, the fact that the majority of patients were male, differences in the length of time on risperidone treatment, and the use of SSRIs complicate the results.[18] Although a risperidone-alone control group was not examined, the mean prolactin level for the combination therapy group was consistent with the mean prolactin results in a study by Kearns and others[19] (mean ± SD for women = 125.0 ± 59.8 ng/mL; for men = 37.3 ± 23.9 ng/mL). The mean dose of clozapine was higher in the combination therapy group and may explain the difference in BMI between the 2 groups. The mean dose of risperidone in the combination therapy group is higher than the average dose of risperidone monotherapy.

Additionally, this study did not examine the incidence of hyperprolactinemia-related side effects. The sexual side effects would have been difficult to interpret secondary to the widespread use of SSRIs in this population. Increasing the availability of serotonin could have an impact on the effects of risperidone and clozapine while stimulating prolactin secretion and reducing the effects of 5-HT$_{2A}$ receptor antagonism.[19] Better-designed prospective studies are indicated to fully understand the impact of the combination of risperidone and clozapine on serum prolactin levels.

Of note, only 2 women (10% of all patients on the combination therapy and 6% of women taking clozapine) were prescribed the combination of clozapine and risperidone. It is possible that our clinicians have chosen to limit the use of this combination therapy in women out of concern related to serum prolactin elevations and associated side effects. Also, because few women were examined, the re-

sults of this study may not generalize to women receiving treatment with combination therapy.

Because patients on combination therapy received a greater mean dose of clozapine, the severity of illness may have had an impact on results. These patients may have been selected for combination therapy because of treatment resistance. Many patients were also treated with SSRIs, which could have affected clozapine levels. Risperidone may also have an impact on serum clozapine levels.[5] Although our previous study found that risperidone did not significantly elevate or reduce serum clozapine levels,[1] Tyson et al.[5] reported an increase in blood clozapine levels from 344 ng/mL to 598 ng/mL 2 weeks after augmentation with risperidone in 1 patient.

There was a significant difference between the 2 groups for weight and BMI; the importance is unclear. We recently reported that clozapine significantly increases weight and that the weight gain may continue for 46 months, but risperidone was not considered as a variable for weight gain.[20] It is possible that risperidone added to clozapine may affect weight gain and BMI, suggesting that weight should be closely monitored in this population when using combination therapy. The combination therapy group received significantly higher doses of clozapine, which may have also had an impact on weight and BMI.

The results indicate that the effect of risperidone on prolactin was dose related and that higher doses resulted in higher serum prolactin levels. This finding is consistent with available information in the literature and supports a clinical intervention of lowering the antipsychotic agent when hyperprolactinemia occurs.[21] The mean dose of risperidone in this study was higher than the average dose of 4.2 mg/day for risperidone monotherapy.[22] In addition, the effect of risperidone on prolactin may reduce over time. It is also possible that clozapine may decrease the prolactin elevation effect of risperidone at lower doses of risperidone.

We have observed that some patients treated with risperidone alone have serum prolactin levels greater than 100 ng/mL. However, we were surprised to observe a narrower range of serum prolactin levels in the combination therapy patients in this study.

Finally, the addition of risperidone to clozapine appears to be a clinically useful intervention to minimize clozapine dose and side effects while producing only moderate elevations in serum prolactin. The management of hyperprolactinemia ultimately must focus on prevention of the long-term physiologic consequences of chronically elevated serum prolactin levels. Patients should be routinely questioned concerning symptoms of elevated prolactin including amenorrhea, reduced libido, impotence, breast enlargement, and lactation. Serum prolactin levels should be drawn at least once after the initiation of combination therapy to determine the impact of adding risperidone to clozapine. Additionally, studies are needed to clarify the risks of long-term elevations of serum prolactin level, specifically on bone density.

Drug names: clozapine (Clozaril and others), fluoxetine (Prozac), paroxetine (Paxil), risperidone (Risperdal), sertraline (Zoloft).

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