Risperidone and Associated Amenorrhea: A Report of 5 Cases

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Background: We report a 5-case series in which risperidone use in usual or lower-than-usual doses was unexpectedly associated with amenorrhea.

Case Reports: On regimens of risperidone (1–8 mg/day), 5 psychiatric patients with various diagnoses developed amenorrhea with elevated serum prolactin levels (mean = 121.7 ng/mL; range, 61.2–229.8 ng/mL). In 4 of 5 cases, menstruation resumed only when risperidone was withdrawn, and in 1 case, menstruation restarted when the dose was tapered. Follow-up serum prolactin levels dropped to a mean of 17.2 ng/mL (range, 6.4–37.6 ng/mL).

Conclusion: These findings indicate that the occurrence of amenorrhea during risperidone treatment may be related to elevated serum prolactin levels. This phenomenon may be due either to the dopamine D_2 blocking effect of risperidone or to the large individual variability in the rate at which risperidone is metabolized.

(J Clin Psychiatry 1999;60:315–317)

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As would be expected from a dopamine-blocking agent, it seemed justified to expect that risperidone, having affinity for dopamine D_2 and serotonin type 2 receptors, also may affect the serum prolactin level and result in prolactin-related effects.

Contrary to the original expectation that haloperidol exhibits more potent D_2 receptor antagonism than risperidone,[1,2] animal research[3] has demonstrated that risperidone is 3 to 5 times more potent than haloperidol in stimulating rat prolactin levels in vivo. In addition, a clinical report[4] indicates that risperidone may increase prolactin to above-normal levels in some patients who are taking standard doses.

Prolactin elevations may be associated with sexual side effects such as galactorrhea, amenorrhea, gynecomastia, and impotence. In premarketing studies of risperidone, the prevalence of risperidone-induced amenorrhea was reported in 1 of 100 to 1 of 1000 women.[5]

To our knowledge, so far there has been only one case report[6] regarding risperidone-induced amenorrhea. Dickson et al.[6] reviewed the charts of 5 premenopausal women with schizophrenia and found that 3 of the 5 women developed galactorrhea, and all 5 developed amenorrhea. The authors suggested that amenorrhea might be associated with high serum prolactin levels associated with risperidone treatment.

In this article, we present 5 cases of psychiatric patients with various diagnoses who developed amenorrhea while on risperidone therapy.

CASE REPORTS

Case 1

Ms. A, a 37-year-old divorced woman with a 3-year history of paranoid schizophrenia, was hospitalized in an acute psychotic state. Subsequent physical examination and laboratory tests revealed no abnormal findings. To control her psychotic symptoms, risperidone alone, 1 mg b.i.d., was initiated and gradually increased to 4 mg b.i.d. over 2 weeks. On the 10th day of risperidone treatment, she developed akathisia, akinesia, muscle rigidity, and hand tremor. Benztropine, 1 mg b.i.d., was added to the regimen of risperidone. On the 62nd day after admission, as she began to gain insight into her illness, she developed depression. Therefore, the antidepressant imipramine was added. On the 94th day after admission, she was discharged with a treatment plan consisting of risperidone, 2 mg b.i.d.; benztropine, 1 mg b.i.d.; and imipramine, 100 mg h.s.

During outpatient department treatment, she first stated that she had not menstruated for 7 months since the start of risperidone therapy, but had concealed it because of a sense of shame. To confirm her surprising statement, we carried out a physical examination and laboratory tests and consulted an obstetrician. On the physical examination, galactorrhea, breast engorgement, and tenderness were found, but other tests did not reveal any abnormal findings. Then, while reviewing her chart, we noticed that she had skipped menstruation during her inpatient

stay. Subsequently, we found that she had an abnormally high serum prolactin level (61.2 ng/mL; normal range, 2.7–19.7 ng/mL). At the time of this examination, she was taking risperidone, 1.5 mg h.s.; benztropine, 1 mg h.s.; and imipramine, 50 mg h.s. Risperidone was then discontinued. Ten days after discontinuation, menstruation resumed and galactorrhea ceased. Her serum prolactin level dropped to 6.4 ng/mL.

Case 2

Ms. B, a 36-year-old woman with schizoaffective disorder, manic type, was admitted to the psychiatric ward. While hospitalized, Ms. B developed akathisia, rigidity, and irregular menstruation on the combined regimen of lithium, 900 mg/day, and haloperidol, 12 mg/day. Therefore, the dosage of haloperidol was gradually tapered to 1.5 mg/day. However, delusional thought persisted, and haloperidol was discontinued and risperidone was initiated. The initial dose of risperidone was 1 mg/day, and the dose was increased to 1.5 mg/day. Five months later, Ms. B first stated that she had no menstruation during the 4 menstrual cycles after the start of risperidone treatment. At that time, her serum level of prolactin was 229.8 ng/mL. The next month, after she discontinued risperidone, menstruation resumed, and her serum prolactin level dropped to 14.5 ng/mL.

Case 3

Ms. C, a 38-year-old woman with bipolar affective disorder, manic type with rapid cycling, was admitted to the psychiatric ward. While in hospital, her medication was lithium, 450 mg b.i.d.; valproic acid, 250 mg b.i.d.; and risperidone, 3 mg b.i.d. Two months later, she was discharged with lithium, 450 mg b.i.d.; valproic acid, 250 mg b.i.d.; and risperidone, 1.5 mg b.i.d. During outpatient treatment, lithium was discontinued. Four months after initiation of risperidone, she reported the absence of menstruation for 3 normal menstrual cycles. At that time, she had galactorrhea and breast engorgement. Her serum prolactin level was 96.1 ng/mL. The next month, after the discontinuation of risperidone, menstruation resumed, galactorrhea ceased, and her serum prolactin level dropped to 7.86 ng/mL.

Case 4

Ms. D, a 28-year-old woman with paranoid schizophrenia, had amenorrhea, galactorrhea, and severe extrapyramidal symptoms occur while taking a high dose of haloperidol (20 mg/day). Therefore, haloperidol was discontinued and risperidone was initiated. Risperidone was initiated at 1 mg b.i.d. and increased gradually to 4 mg b.i.d. over 2 weeks. On the 7th day of risperidone treatment, extrapyramidal symptoms developed, and benztropine, 1 mg b.i.d., was added. The dosage of risperidone was titrated to 2 mg b.i.d. over 2 months. Six months after initiation of risperidone, she reported the absence of menstruation during 3 normal menstrual cycles while taking risperidone. During the physical examination, galactorrhea and breast engorgement were found. At that time, her serum prolactin level was 119.3 ng/mL. Subsequently, the dose of risperidone was decreased over 1 month to 1 mg/day, but amenorrhea persisted and the serum level of prolactin was still high (104.6 ng/mL). Eventually, risperidone was discontinued. The following month, her menstruation resumed, and her serum prolactin level dropped to 20 ng/mL.

Case 5

Ms. E, a 30-year-old woman with a 5-year history of schizoaffective disorder, was admitted in a manic state to the psychiatric ward. Previously, she had been admitted several times to the hospital and treated with lithium (900–1200 mg/day) and haloperidol (2–10 mg/day). While taking the combined regimen, she developed an involuntary orolingual movement. At admission, haloperidol was discontinued and risperidone and lithium were initiated. The dose of risperidone was initially 1 mg b.i.d. and was increased gradually 4 mg b.i.d. over 2 weeks. One month later, Ms. E developed subclinical hypothyroidism. Lithium was then switched to valproic acid, 500 mg b.i.d. Three months later, she was discharged taking valproic acid, 500 mg b.i.d., and risperidone, 4 mg b.i.d. After discharge, she reported that she had not menstruated for 3 menstrual cycles while an inpatient. At that time, her serum prolactin level was 102.2 ng/mL. The risperidone treatment was then tapered over 1 month to 1 mg/day. Since then, menstruation resumed and her serum prolactin level dropped to 37.6 ng/mL.

DISCUSSION

Amenorrhea is defined as the absence of menstruation for 3 consecutive cycles or 3 cycles over 6 months in a woman who has previously menstruated.[7] Our 5 cases met this definition.

Our experience accords with the case report of Dickson et al.[6] The fact that serum prolactin levels returned to normal after discontinuation of risperidone treatment, and that menstruation resumed, strongly supports that the amenorrhea was related to the risperidone treatment.

However, we can not explain why amenorrhea occurred at usual or lower-than-usual doses of risperidone (1–8 mg/day). One possible explanation is that risperidone may have high dopamine D_2 occupancy, in line with conventional neuroleptics. Positron emission tomography (PET) studies in schizophrenic patients indicate that 3–4 mg/day of risperidone results in about 80% to 90% D_2 blockade, which might result in prolactin-related effects.[8] Moreover, Bowden et al.[3] demonstrated that 5-HT_2 recep-

tor antagonism of risperidone did not modulate the dopaminergic regulation of prolactin release either in vitro or in vivo. Furthermore, a single photon emission computed tomography (SPECT) study,[9] which showed that plasma prolactin levels were positively associated with D_2 receptor occupancy in vivo, supports this assumption.

Another possibility is that our patients may have a large individual variability in the rate at which risperidone is metabolized and the potential for drug interactions. Risperidone undergoes extensive first-pass hepatic metabolism by cytochrome P450 (CYP) isoenzyme CYP2D6 to the metabolite 9-hydroxyrisperidone, which has comparable biological activity.[10] The enzyme is polymorphically expressed with "slow metabolizers" (commonly identified by the extent of dextromethorphan or debrisoquin metabolism in vivo), identifiable in 7% of the white (Swedish) population.[11] In subjects receiving risperidone, a slow dextromethorphan-metabolizing status has been associated with a 7-fold reduction of clearance, an increase in the area under curve (AUC), and a prolonged half-life from about 3 hours in rapid metabolizers to 22 hours in slow metabolizers.[12] From this point of view, drug interactions in slow metabolizers may have led to the amenorrhea in low doses.

These data, though limited, have several considerations worthy of discussion. First, our patients were taking concomitant drugs in addition to risperidone. For example, in case 1, imipramine was added to the regimen of risperidone; in case 2, lithium was added; and in cases 3 and 5, valproic acid was added. Therefore, various combinations of drugs may affect pharmacodynamic and pharmacokinetic interactions of risperidone, which can result in adverse effects. However, in practice, investigators did not differentiate efficacy and adverse reactions occurring with risperidone monotherapy from those occurring with several different combinations of mood stabilizers and risperidone in bipolar disorder patients.[13,14] Also there was a report that a tricyclic antidepressant, amitriptyline (100 mg/day), did not affect the mean serum concentration of risperidone.[15] Accordingly, the possibility of amenorrhea due to polypharmacy is unlikely.

Second, in case 4, in spite of switching the patient from haloperidol treatment to risperidone treatment, amenorrhea occurred again. The patient experienced amenorrhea while taking haloperidol. In such a case, it is desirable to consider a trial of clozapine or olanzapine. There have been reports that clozapine does not elevate plasma prolactin level[16] and that olanzapine shows less prolactin elevation than do conventional antipsychotics or risperidone.[17]

In clinical practice, the occurrence of amenorrhea may be one reason for noncompliance; thus, clinicians should be vigilant to such side effect problems during risperidone treatment.

Drug names: amitriptyline (Elavil and others), benztropine (Cogentin and others), clozapine (Clozaril), haloperidol (Haldol and others), imipramine (Tofranil and others), olanzapine (Zyprexa), risperidone (Risperdal), valproic acid (Depakene and others).

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