

Effect of Risperidone on Prolactinoma Growth in a Psychotic Woman

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Objective: The case of a psychotic woman is described in which risperidone use was found to correspond with an increase in the size of a prolactinoma and prevented the return of serum prolactin level to baseline. **Methods:** Although the patient had been treated with a high dose of bromocriptine, her prolactin level remained elevated, causing persistent galactorrhea. The patient later was treated with olanzapine and carbamazepine successfully. **Results:** This case report highlights the role of risperidone on prolactin and discusses alternative methods of treating psychosis when the etiology is unclear, especially in younger patients. **Conclusions:** The authors recommend that additional studies regarding the relationship between the growth of prolactinoma and atypical antipsychotics would be worthwhile. **Key words:** psychosis, prolactinoma, atypical antipsychotic.

D2 = dopaminergic; EEG = electroencephalogram; MRI = magnetic resonance imaging; GABA = gamma-aminobutyric acid.

It has been well established that conventional neuroleptic medications (phenothiazines and butyrophenones) cause an increase in serum prolactin levels (1–3). Patients who have been continuing long-term maintenance doses of neuroleptics, have an average of a three- to four-fold increase in baseline prolactin levels (1) with ranges of up to 19 times the mean baseline values (4). It has been reported that a girl with schizophrenia developed prolactinoma while being treated with thioridazine (5). Thioridazine may have also enhanced prolactinoma growth as manifested by an increase in serum prolactin concentration and deterioration of visual fields in a man with schizophrenia (6). In another case, a woman with a proven prolactinoma became acutely psychotic (7). The clinical effects of increased prolactin levels are not well understood, but there is some evidence that increases in serum prolactin may be associated with several psychiatric disorders, including depression, hostility, premenstrual syndrome, and alcoholism (8–10). Because a dopamine agonist can induce shrinkage of prolactinomas, dopamine antagonists such as thioridazine might be expected to result in tumor growth (11). Among the atypical neuroleptics, clozapine does not affect prolactin secretion because of its weak effects on D2 receptors (12–13). Risperidone produces dose-related increases in plasma prolactin levels in men and women (14–15). Hardan et al. (16) conducted a clinical trial with risperidone in 20 children and adolescents with

developmental disorders. Galactorrhea developed in two of the seven girls enrolled in the trial, although the risperidone ranged from 1.5 to 10 mg/day. One of these girls also developed amenorrhea which resulted in risperidone discontinuation.

In a letter to the editor, Dickson et al. (17) reported an increase in prolactin levels in five premenopausal women with schizophrenia while taking risperidone, resulting galactorrhea in three and amenorrhea in all five patients. After risperidone discontinuation, galactorrhea ceased in all the three patients and menses resumed in three of the patients. In a randomized, controlled clinical trial, olanzapine—even at the highest doses used—was not associated with persistent elevations of prolactin (18). The analysis of the plasma prolactin concentrations obtained during the trials in schizophrenic patients revealed that the newest atypical neuroleptic quetiapine did not differ from placebo in its effect on plasma prolactin after up to 6 weeks of treatment and did not cause any sustained elevation of prolactin in these patients (19). The following case report will highlight the long-term effect of risperidone on the growth of a prolactinoma in a psychotic woman.

CASE REPORT

A 19-year-old, single, African American woman (Ms P.), without any known previous psychiatric illness, started experiencing visual, olfactory, and auditory hallucinations (frequently, command in nature), along with a generalized headache in September 1996. She also reported having psychosensory features (deja vu, derealization, depersonalization) associated with frequent functional hallucinations (hearing voices during flushing the toilet, running tap water, running engine of a bus and car). The voices and headaches made her depressed, and she was unable to concentrate in her studies. She stopped going to school and was spending most of her time in her room. Her sleep, appetite, and energy were also impaired during this time. The vision of her right eye was poor before (20/100), but gradually it was becoming worse. The patient denied any severe mood swings, any manic or hypomanic episode, or taking any street drugs while she was not feeling well.

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No suicidal ideation had been reported by her. The patient's family and the patient also denied any seizure around this time. The patient was treated only with acetaminophen and aspirin, which relieved her headache for a short period of time.

Four months later in January 1997, Ms P. was hospitalized in the psychiatric unit because she suddenly became violent and attacked neighbors and family members without any provocation. Her psychosis also increased at this time. During her hospitalization, she remained incontinent of her menses and urine, had persistent psychosensory features, and was unable to recall the incident leading to her hospitalization. The patient originally was treated with haloperidol, lorazepam, and benztropine, but later was switched to 1 mg of oral risperidone twice daily and 250 mg of oral Depakote twice daily. The patient had a questionable episode of seizure while she was in the hospital. Her laboratory results revealed high prolactin values, 260.8 ng/ml ($N = 20$ ng/ml). The EEG in January 1997 showed sharp transients on the left temporal area, but no clear epileptiform discharges were noted. The MRI of her brain in January 1997 reported a pituitary adenoma (10–11 mm in diameter) with a degree of optic chiasm compression. The patient was discharged with instructions to take 25 mg of oral bromocriptine every day, 250 mg of oral Depakote three times a day, 1 mg of oral risperidone three times a day, and 1 mg of oral Cogentin every day because she was psychiatrically stable.

After discharge, she had been followed by the psychiatrist, endocrinologist, and neurologist. Ms P. was aware of a milky secretion from her breasts and dysregulation of her menstrual cycles inasmuch as she had been diagnosed as having a pituitary tumor. The hallucinations decreased and the patient was able to function in her daily activities. Repeat MRIs and serum prolactin levels were done at scheduled intervals (two times a year). The patient remained stable for 2 years after her first hospitalization. Because no epilepsy was found on a repeat EEG, her therapeutic regimen of Depakote was discontinued a few months after her discharge, and she continued with 4 mg of oral risperidone every day, 1 mg of oral benztropine every day, and 5 mg of oral bromocriptine three times a day. In April 1999, the patient was hospitalized a second time for 2 weeks for demonstrating behavior similar to her initial episode. This time, the MRI showed that the prolactinoma had increased to 12 mm and the prolactin level had decreased to 45 ng/ml. Her vision in the right eye became 20/400, and she had an occasional headache along with the psychosis. The patient was started on a regimen of 5 mg of olanzapine every night and 200 mg of carbamazepine three times

a day, while her dosage of risperidone was tapered. The prolactin level was lowered to 35 ng after 1 month, but there was no change in size of the prolactinoma in the repeat MRI. The MRI did not show any midline shift. The repeat EEG did not show any significant change from the previous one. The patient is stable currently, and the hallucinations have been decreased. Ms P. is no longer complaining of galactorrhea. Her menstrual cycle is becoming regular, and the headache has decreased. She is able to perform reasonably well in her daily and academic activities. The patient is currently being maintained on a regimen of 5 mg of oral olanzapine every night, 400 mg of oral carbamazepine twice a day, 5 mg of oral bromocriptine three times a day, and 1 mg of oral benztropine every day without any significant clinical side effects.

DISCUSSION

This case report suggests that long-term maintenance on risperidone was linked to the persistent elevation of the prolactin level from the baseline. The long-term effect of risperidone also could be responsible for the enlargement of the pituitary adenoma in this patient, inasmuch as previous case reports suggest the role of conventional antipsychotics in induction or enhancement of growth of pituitary adenomas. The increased growth of the adenoma does collaborate with the decreased acuity of vision in the right eye of our patient causing severe visual impairment. Although she has been receiving a high dose of bromocriptine, the adenoma did increase in size. The serum prolactin level decreased after the patient was switched to olanzapine. Depakote was discontinued because of the increase in the prolactin level, because the patient already had hyperprolactinemia. Controlled clinical trials report that in prolactinomas, the prolactin level increases paradoxically after a high dose of Depakote (≥ 800 mg) suggesting the existence of a pituitary resistance to GABA (20). Carbamazepine was added later to the regimen because some features of her psychosis were suggestive of temporal lobe epilepsy, and it is not known to increase the level of prolactin (21). Remember the possibility of a seizure, even though the EEG was nonconfirmatory, particularly in younger patients with early onset of psychosis because the EEG has a low yield in diagnosing epilepsy.

Anticonvulsants or mood stabilizers would be an alternative in these patients, just as carbamazepine was helpful in our case. Reductions in cortical and trabecular bone mass have been documented in young women with hyperprolactinemic amenorrhea (22, 23), and clinicians who deal with patient populations con-

sisting of young women may be interested. Animal studies have shown that prolactin could be an initiator or a promoter of breast carcinoma, whereas human studies are inconclusive (24). Because case reports (25) have suggested an association of breast cancers and prolactinoma, we should be careful about carcinomas of the breast. Although some studies report the use of clonidine or propranolol to treat psychosis, these medications should be considered carefully because of their other side effects. In treating patients with the newer atypical antipsychotics, one must be concerned about the prolactin level either iatrogenically elevated by medication or resulting from a prolactin secreting adenoma.

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