CASE REPORT

Use of the dopamine agonists bromocriptine and cabergoline in the management of risperidone-induced hyperprolactinemia in patients with psychotic disorders[1]

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ABSTRACT. Risperidone is a novel antipsychotic agent that blocks both dopaminergic and serotonergic receptors. In several reports, clinically significant hyperprolactinemia has been reported in patients on this agent. However, the optimal management of risperidone-induced hyperprolactinemia has not been clarified. We reviewed the records of 5 patients with psychotic disorders who were evaluated for risperidone-induced hyperprolactinemia. There were 4 females and 1 male patient, aged 30-45 yr. All patients had significant hyperprolactinemia, with prolactin (PRL) levels ranging from 65.5 to 209 µg/l. All but 1 of these patients had manifestations of hypogonadism. In these 4 patients, risperidone therapy was continued and the dopamine agonists bromocriptine or cabergoline were added. In 3 out of 4 patients, such additional therapy reduced the PRL level and alleviated hypogonadism. None of the patients treated with these agents had a worsening of psychosis. We conclude that risperidone can cause clinically significant hyperprolactinemia in patients treated with this drug. If risperidone therapy must be continued in such patients, addition of the dopamine agonists bromocriptine or cabergoline may successfully alleviate hyperprolactinemia and the associated manifestations without worsening psychotic symptoms.

(J. Endocrinol. Invest. *23:* 765-770, 2000)

INTRODUCTION

Drug-induced hyperprolactinemia is a commonly encountered clinical problem. Although many different medications have been reported to cause hyperprolactinemia, the psychotropic (neuroleptic) medications remain the most common agents causing this problem. Most medications that cause hyperprolactinemia block the action of dopamine, which is the prolactin (PRL) inhibiting hormone released by the hypothalamus into the portal circulation and transported to the anterior pituitary gland. PRL secretion is unique among the anterior pituitary hormones in that it is under primarily inhibitory control by dopamine. Therefore, any drug which blocks the action of dopamine or reduces dopamine levels in the anterior pituitary gland has the potential to cause hyperprolactinemia (1, 2).

Drug-induced hyperprolactinemia may be clinically insignificant, in which case nothing needs to be done other than continued patient follow-up. However, clinically significant manifestations can occur, including bothersome galactorrhea and menstrual disturbances in females and symptomatic hypogonadism in males. Although gonadal steroids can be given to correct hypogonadism in these patients, alleviation of hyperprolactinemia is necessary for treatment of galactorrhea. When these manifestations occur, the optimal approach is either to reduce the dose of the medication or if possible to discontinue the offending medication and substitute another in its place. However, the patient's underlying disorder may not allow for this. In this case, another approach that has been used successfully to alleviate hy-

[1]Portions of this work were presented at the 79th Annual Meeting of the Endocrine Society, June 11-14, 1997, Minneopolis, Minnesota.

Key-words: Risperidone, hyperprolactinemia, dopamine, bromocriptine, cabergoline.

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Accepted May 31, 2000.

perprolactinemia is the addition of a dopamine agonist such as bromocriptine or amantadine (1, 2).

Risperidone is an agent that has come into increased usage in recent years in the management of various psychotic disorders. It is considered an atypical antipsychotic agent and is a member of a new chemical class, the benzisoxasole derivatives. Risperidone is known to antagonize both dopaminergic and serotonergic (5-HT) receptors, particularly those of the D_2 and 5-HT_2 subclasses (3). Although it is associated with much less extrapyramidal side effects than older neuroleptic drugs, its potential to cause hyperprolactinemia in both males and females appears to be equal to or greater than these older drugs (4-6). Several reports have described reversible, symptomatic hyperprolactinemia in both male and female patients on this drug (5-12). In our own practice, risperidone has become a leading cause of drug-induced hyperprolactinemia. We have therefore chosen to describe our own experience with several patients who were referred to us for the evaluation and management of risperidone-induced hyperprolactinemia.

CASE REPORTS

The following is a description of 5 patients with the diagnosis of chronic psychosis who were referred to us for evaluation of hyperprolactinemia while on risperidone therapy between 1994 and 1998. All were in-patients at a chronic care facility and had their psychiatric status monitored on a daily basis. The pertinent clinical features of these 5 patients are summarized in Table 1.

Case 1

A 36-year-old female was being treated with risperidone at a dose of 9 mg/day for a psychotic disorder. She was referred for oligomenorrhea associated with a PRL level of 185 µg/l (normal range, 3-24 µg/l). Physical examination revealed no galactorrhea. She had normal renal, hepatic, and thyroid function. A pituitary magnetic resonance imaging (MRI) scan revealed no evidence of any pituitary or hypothalamic tumor. Because of her underlying psychiatric disorder, risperidone was continued and bromocriptine was added to her regimen. Bromocriptine was initiated at 2.5 mg/day and titrated in increments of 2.5 mg up to a dose of 25 mg/day. PRL levels were taken approximately 4 weeks after bromocriptine dose adjustments. She had no worsening of her psychotic symptoms, however her PRL levels remained significantly elevated at 145 µg/l, and she continued to have oligomenorrhea. Ultimately, bromocriptine therapy was discontinued and estrogen replacement therapy was added.

Case 2

A 30-year-old female was being treated with risperidone at a dose of 5 mg/day for a psychotic disorder. She was referred for evaluation of oligomenorrhea associated with a PRL level of 74 µg/l. Physical examination revealed no galactorrhea. She had normal renal, hepatic, and thyroid function. A pituitary MRI scan revealed no evidence of any pituitary or hypothalamic tumor. Because of her underlying psychiatric disorder, risperidone was continued and bromocriptine was added to her regimen. Bromocriptine was initiated at 2.5 mg/day and titrated upwards in increments of 2.5 mg/day. PRL

Table 1 - *Characteristics and responses to dopamine agonist therapy of patients with psychotic disorders and risperidone-induced hyperprolactinemia.*

Patient	Age, sex	Risperidone dose (mg/day)	Initial PRL level (µg/l)*	Symptoms	Treatment	PRL level (µg/l) following treatment and outcome**
1	36 F	9	185	oligomenorrhea	bromocriptine 25 mg/day	PRL 145, continued oligomenorrhea
2	30 F	5	74	oligomenorrhea	bromocriptine 7.5 mg/day	PRL 28, normal menses
3	29 F	5	209	amenorrhea	bromocriptine 10 mg/day	PRL 53, normal menses
4	30 F	5	72	none	none	-
5	45 M	5	65.5	low testosterone	cabergoline 0.5 twice a week	PRL 48.2, normalization of testosterone

*Normal prolactin (PRL) levels for female subjects 3-24 µg/l, for male subject 1.6-18.8 µg/l; **none of the patients who received dopamine agonist therapy experienced worsening of psychotic symptoms.

levels were repeated approximately 4 weeks after each adjustment in the bromocriptine dose. Her PRL levels fell to 28 µg/l on 7.5 mg/day of bromocriptine, and within several months her menses subsequently normalized. She experienced no worsening of her psychotic symptoms on bromocriptine.

Case 3

A 29-year-old female was being treated with risperidone at a dose of 5 mg/day for a psychotic disorder. She was referred for the evaluation of amenorrhea associated with a PRL level of 209 µg/l. Physical examination revealed no galactorrhea. She had normal renal, hepatic, and thyroid function. A pituitary MRI scan revealed no evidence of pituitary or hypothalamic tumor. Because of her underlying psychotic disorder, risperidone was continued and bromocriptine was added to her regimen. Bromocriptine was initiated at 2.5 mg/day and was titrated upwards in increments of 2.5 mg/day. PRL levels were repeated approximately 4 weeks after each adjustment in the bromocriptine dose. On 10 mg/day of bromocriptine, her PRL level fell to 53 µg/l, and within several months her menses normalized. She experienced no worsening of her psychotic symptoms on bromocriptine.

Case 4

A 30-year-old female was being treated with risperidone at a dose of 5 mg/day for a psychotic disorder. She was found to have a PRL level of 72 µg/l. She denied any history of menstrual disturbance or galactorrhea. Physical examination revealed no galactorrhea. She had normal renal, hepatic, and thyroid function. A pituitary MRI scan revealed no evidence of any pituitary or hypothalamic tumor. Since she had no symptoms referable to her hyperprolactinemia, risperidone therapy was continued unaltered and she was followed without additional therapy.

Case 5

A 45-year-old male was being treated with risperidone at a dose of 5 mg/day for a psychotic disorder. He was found to have a PRL level of 65.5 µg/l (normal range, 1.6-18.8 µg/l) and was referred for evaluation. He denied symptoms of hypogonadism or galactorrhea. Physical examination revealed no galactorrhea and a normal testicular examination. Laboratory evaluation revealed a slightly reduced free testosterone level of 28.1 pmol/l (normal range, 45.1-139.6 pmol/l) and an inappropriately low LH level of 1.9 IU/l (normal range, 1.5-9 IU/l). He had normal renal, hepatic and thyroid function. Because of his underlying psychotic disorder, risperidone was continued and cabergoline, a new dopamine agonist that is longer acting and more potent than bromocriptine (13), was added to his regimen. Cabergoline was initiated at a dose of 0.25 mg twice a week and titrated upwards in increments of 0.25 mg/week. PRL levels were repeated approximately 4 weeks after each adjustment in the cabergoline dose. Within several months on 0.5 mg twice a week of cabergoline, his PRL level fell to 48.2 µg/l, and his free testosterone level rose to a normal level at 53.7 pmol/l. He experienced no worsening of his psychotic symptoms on cabergoline therapy.

DISCUSSION

These cases demonstrate several important features of risperidone-induced hyperprolactinemia. It is clear from this series as well as from previous reports that risperidone may cause a significant elevation in the PRL levels in both male and female patients when at dosages used to treat patients with psychotic disorders (5-12). Hyperprolactinemia has been reported with risperidone doses as low as 1.5 mg/day (10). Although PRL levels of greater than 200 µg/l are usually considered strong evidence for the presence of a PRL secreting pituitary tumor, one of our patients (Case 3) had a PRL level of 209 µg/l, and another (Case 1) had a PRL level of 185 µg/l. Other reports have described PRL levels over 200 µg/l in patients on risperidone treatment (9, 10). Furthermore, the degree of hyperprolactinemia is variable and does not correlate with the risperidone dose. One of our patients (Case 2) was observed to have a PRL level of 74 µg/l on 5 mg/day of risperidone, whereas another patient (Case 3) had a PRL level of 209 µg/l on exactly the same dose. A previous study by Luis De Rivera *et al.* (14) looking at PRL levels in patients on older neuroleptic agents also showed that the degree of hyperprolactinemia does not correlate well with the dose of medication. In this study, the degree of hyperprolactinemia correlated better with patient age, sex, and duration of therapy, with females, younger patients, and patients receiving acute therapy having higher PRL levels than males, older patients, and patients receiving chronic therapy with neuroleptics. A more recent study also found a poor correlation between the risperidone dose and the level of hyperprolactinemia (15). Huang *et al.* (4) showed that the degree of hyperprolactinemia in healthy subjects on risperidone correlates with serum risperidone levels. Therefore, individual variation in risperidone metabolism may explain why patients on similar doses of risperidone may have widely different PRL levels.

We have found that the clinical manifestations of patients with risperidone-associated hyperprolactinemia are variable and do not always correlate well with the degree of hyperprolactinemia. Some patients may remain asymptomatic despite a significant elevation in the PRL level, whereas others may develop signs or symptoms of hypogonadism and/or galactorrhea despite a much lower level. Kleinberg *et al.* (15) also demonstrated a poor correlation between the serum PRL level and clinical symptoms. This could reflect a varying sensitivity in patients to the gonadotropin suppressing effects of PRL.

We have shown that the addition of the dopamine agonists bromocriptine and cabergoline may be successful in reducing the level of hyperprolactinemia and alleviating symptoms in some, but not all patients on risperidone therapy. In our series, these agents reduced the level of hyperprolactinemia in all 4 patients in which they were used for this purpose, and, in all but 1 of these patients, such therapy reversed associated hypogonadism. It is also important to note that complete normalization of the PRL level is not necessary for improvement in clinical symptoms to occur, as shown in Cases 3 and 5. In those patients who did respond to these agents, we were able to use relatively modest doses with good results.

Because dopamine excess is thought to play a major role in the pathogenesis of psychotic disorders, we were initially concerned that the use of dopamine agonists in these patients might worsen their underlying mental state. Indeed, bromocriptine has been reported to cause hallucinations and other neuropsychiatric disturbances in a small percentage of patients treated with this agent for various hormonal disorders (16). Happily, the addition of bromocriptine or cabergoline to risperidone therapy did not result in an increase in psychotic symptoms or adversely affect the mental status of any of our patients whom we chose to treat with these agents, including 1 patient who received 25 mg/day of bromocriptine. Previous studies have shown that modest doses of bromocriptine may be safely given to patients who have symptomatic hyperprolactinemia on older neuroleptic agents without exacerbating psychosis. Beaumont *et al.* (17) gave bromocriptine at a dose of only 2.5 mg/day to patients with symptomatic hyperprolactinemia secondary to older phenothiazine agents. In most of these patients, a reduction in PRL levels was observed in association with improvements in galactorrhea without any worsening in psychotic symptoms. Varia *et al.* (18) reported that bromocriptine at a dose of 5 mg/day successfully alleviated both hyperprolactinemia and galactorrhea in a patient on haloperidol without exacerbating psychosis. Shenoy *et al.* (19) used 10 mg/day of bromocriptine to successfully treat haloperidol-induced hyperprolactinemia in a patient with schizophrenia. The patient did not experience an increase in psychotic symptoms on bromocriptine therapy. We are aware of only one other published report in which bromocriptine was used in the management of risperidone-induced hyperprolactinemia. In a report by Popli *et al.* (9), two patients with hyperprolactinemia and galactorrhea secondary to risperidone were reported. One patient was switched to thioridazine with improvement in galactorrhea, whereas bromocriptine at a dose of 5 mg/day was added to the other patient's regimen with some improvement in hyperprolactinemia and galactorrhea, although amenorrhea persisted. No increase in psychotic symptoms was noted in the patient who received bromocriptine.

In addition to bromocriptine, another agent that has been used successfully in the management of drug-induced hyperprolactinemia in patients with psychotic disorders is amantadine, which is also considered to be a dopamine agonist. Amantadine at doses of 200-300 mg/day has been given to patients with symptomatic hyperprolactinemia secondary to older neuroleptic agents and has been shown to successfully lower PRL levels in these patients without exacerbating psychosis (20, 21). Therefore, it appears from several studies, in addition to our own, that agents with intrinsic dopamine agonist activity can be safely given to patients with psychotic disorders who have medication-induced hyperprolactinemia as long as the antipsychotic medication is continued.

Another option in the management of risperidone-induced hyperprolactinemia is substitution of another antipsychotic medication. In a study by Breier *et al.* (12), clozapine, another atypical antipsychotic agent, caused significantly less hyperprolactinemia than risperidone while having greater antipsychotic activity. Other PRL sparing antipsychotic drugs include onlanzipine and quetiapine (2). Finally, there is one recent case report of a patient with risperidone-induced hyperprolactinemia and amenorrhea who demonstrated a reduction in the serum PRL level and resumption of normal menses after being given a Japanese herbal medicine, shakuyaku-kanzo-to (22). The mechanism by which this herb may act to reduce hyperprolactinemia is unclear.

The patients we saw were institutionalized because of their psychiatric condition. Despite their menstrual disturbances, infertility was not an important issue for the female patients, and the male patient did not

complain of symptomatic hypogonadism, which was diagnosed solely on the basis of blood tests. However, it is important to recognize that there are other potential adverse consequences of long-standing hypogonadism secondary to hyperprolactinemia that might manifest themselves in patients on chronic antipsychotic medication. One such consequence is loss of bone mineral density with resulting osteoporosis and an increased susceptibility to fracture. This is a particularly relevant issue for bedridden institutionalized patients, since such patients often get little exercise, may have poor dietary intake of calcium and vitamin D, and may have reduced exposure to sunlight, thus further impairing vitamin D metabolism. Previous studies in both female and male patients with hyperprolactinemia due to PRL-secreting pituitary adenomas have demonstrated reduced bone mineral density that often improves following correction of hyperprolactinemia (23). In addition, there is also evidence that patients with neuroleptic-induced hyperprolactinemia can manifest loss of bone mineral density (24, 25). Therefore, it is important to correct hypogonadism secondary to drug induced hyperprolactinemia in these patients to attempt to prevent loss of bone mineral content, even when infertility and loss of libido are not relevant issues for the patient. In a report by Kartaginer *et al*. (25), a patient with neuroleptic-induced hyperprolactinemia was found to have a reduction in bone mineral density in both the spine and the femur that improved following use of bromocriptine. In addition, in women, estrogen has a cardioprotective effect, and reduced levels of estrogen in patients with longstanding hyperprolactinemia might increase the risk of coronary artery disease in such patients (23). Therefore, the potential consequences of hyperprolactinemic-induced hypogonadism on both the skeletal and the cardiovascular systems must be considered when dealing with these patients, and provide strong arguments for correction of the hypogonadal state, even in asymptomatic patients and patients who are not concerned about fertility.

In summary, risperidone can cause substantial hyperprolactinemia in treated patients that may or may not be associated with symptoms. Therefore, all patients on risperidone therapy should be followed for the development of clinically significant hyperprolactinemia. Our cases suggest that addition of dopamine agonists in the form of bromocriptine or cabergoline is an effective option in the management of symptomatic patients with risperidone-induced hyperprolactinemia, and that such therapy is unlikely to exacerbate psychosis. However, further studies with larger numbers of patients followed over a longer period of time will be necessary before such therapy can be recommended on a widespread basis.

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