Cabergoline Treatment of Risperidone-Induced Hyperprolactinemia: A Pilot Study

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Background: D_2 blockers, including the atypical antipsychotic risperidone, induce hyperprolactinemia in a significant number of patients treated. The endocrine and sexual side effects related to hyperprolactinemia significantly impair tolerability and compliance in patients, including those with a good response to risperidone. This pilot study aimed to evaluate the efficacy and tolerability of a low dose of cabergoline, a D_2 agonist, in the treatment of risperidone-induced hyperprolactinemia.

Method: Nineteen male and female DSM-IV–defined schizophrenic patients who were clinical responders to risperidone but were suffering from symptomatic hyperprolactinemia were treated with cabergoline, 0.125 to 0.250 mg/week for 8 weeks. Plasma prolactin level was assessed at baseline and at the end of the study. Data were collected from January 2002 to April 2003.

Results: After cabergoline treatment, the mean decrease in plasma prolactin levels was statistically significant ($p < .05$) for the total sample, and 11 patients showed remission of clinical signs with prolactin values within the normal range. No side effect was observed or reported, and the patients' psychopathology was unchanged.

Conclusions: Results suggest that low-dose cabergoline treatment of risperidone-induced hyperprolactinemia may be safe and clinically effective in a relevant number of patients.

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A number of recent extensive reviews have well addressed[1–3] the problem of antipsychotic-induced hyperprolactinemia and its short- and long-term clinical consequences. New antipsychotics have not eliminated this problem, particularly those with prominent dopamine-blocking properties, such as the serotonin/dopamine antagonist risperidone.[4] Controlled studies with risperidone doses of up to 6 mg/day reported 8% to 9% prevalence of sexual and endocrinologic side effects among women,[4] 8% to 15% prevalence of erectile and ejaculatory dysfunction among men, and 2% to 12% prevalence of decreased libido among both sexes.[4]

Dose reduction, the first-line strategy for combating these side effects, is not always effective in abating hyperprolactinemia and its clinical signs and may lead to acute recurrence of psychosis. Usually, if this strategy is ineffective and prolactin-related side effects are intolerable, patients are switched to another antipsychotic with lower D_2 antagonism, such as olanzapine, clozapine, or quetiapine. Nevertheless, the risk of agranulocytosis reduces the clozapine therapeutic index if hyperprolactinemia is the only indication. Moreover, clozapine and olanzapine were recently suggested to convey a higher risk of weight gain and diabetes than risperidone.[5,6] A recent study switching 5 risperidone-treated hyperprolactinemic patients to quetiapine, a drug considered usually devoid of endocrine effects[7] (but with a recent report of hyperprolactinemia[8]), concluded that switching to quetiapine could be a safe strategy to reduce prolactin and maintain clinical efficacy, but the sample was too small to generalize conclusions.[9] In summary, due to the side effect profile of alternative antipsychotics and the limited clinical data, switching individuals from risperidone to obtain a better "global" tolerability outcome is not warranted (the result may be a switch from one side effect to another). This problem is more relevant if the patient is a full responder to risperidone and hyperprolactinemia is the only clinically significant side effect. In these cases, another possible strategy would be to use dopamine agonists, but the fear of exacerbating psychotic symptoms and the insufficient data in the literature limit this practice.[1]

Cabergoline is an ergot derivative with a long half-life and with clinical efficacy and tolerability at doses varying from 0.5 to 1 mg/week. Cabergoline was found to

be superior to bromocriptine in treating primary and secondary hyperprolactinemia.[10] Its liability to induce psychotic symptoms has not yet been directly assessed, but no psychotic worsening or exacerbation was reported in 2 very small case series of psychotic adults[11] and children[12] with risperidone-induced hyperprolactinemia. The aim of the present study was to assess the efficacy and tolerability of a low dose of cabergoline used to treat symptomatic hyperprolactinemia in a sample of schizophrenic patients fully responsive to risperidone.

METHOD

The sample consisted of 6 male and 13 nonmenopausal female schizophrenic outpatients diagnosed according to DSM-IV criteria. Inclusion criteria were symptomatic hyperprolactinemia occurring during effective risperidone treatment and the documented failure of a previous dose reduction to abate hyperprolactinemia symptoms. Hyperprolactinemia was defined as a plasma prolactin concentration over 18 ng/mL for men and 29 ng/mL for women (according to the hospital reference ranges of normality, adopting those based on 661 normal controls, included in the Chiron Diagnostics Ready Pack analysis kit used [Chiron Diagnostic Corporation, East Walpole, Mass.]). To define hyperprolactinemia as "symptomatic," the laboratory finding had to be associated with a score of at least 2 (certainly present side effect) on at least 1 item among those included in the endocrinologic side effect subscale of the UKU Side Effect Rating Scale[13] and related to prolactin elevation (amenorrhea, oligomenorrhea, galactorrhea, gynecomastia, decreased libido, erectile dysfunction). All patients included in the study had shown a full clinical response to risperidone only for at least 6 months and documented nonresponse to other classical and atypical antipsychotics. Informed consent to participate in this experimental trial was obtained after a complete explanation of the aims, procedures, possible benefits, and risks of the treatment (with detailed explanation of the risk of psychotic symptoms worsening). Data were collected from January 2002 to April 2003.

Plasma prolactin level was assessed with a chemiluminescence analytic method (ACS Centaur, Chiron Diagnostics Ready Pack) on blood samples obtained with antistress procedures before and after 8 weeks of cabergoline treatment, both at 8:00 a.m. Treatment was started with a cabergoline dose of 0.125 mg once a week (1/4 of a 0.5-mg tablet) as add-on treatment to risperidone monotherapy, given at previously stabilized doses (at least 2 months of unchanged dose). Cabergoline dose could be doubled if symptoms of hyperprolactinemia were unchanged after 4 weeks, while the risperidone dose had to remain unchanged throughout the 8 weeks of cabergoline add-on treatment. Clinical symptoms of hyperprolactinemia were reassessed by means of the UKU at the end of the 8 weeks of treatment. Psychiatric symptoms were assessed by means of the Brief Psychiatric Rating Scale[14] before and after the end of the 8 weeks of treatment with cabergoline. Patients were also followed up, with monthly evaluations, to assess the course of clinical signs of hyperprolactinemia and psychopathology after the end of treatment.

Table 1. Clinical, Demographic, and Treatment Characteristics of the Sample[a]

Patient	Sex	Age (y)	Risperidone Dose (mg/d)	Basal Prolactin Level (ng/mL)	Final Prolactin Level (ng/mL)
1	F	24	2	84	1
2	F	39	3	216	159
3	F	40	3	179	100
4	F	32	3	140	120
5	F	35	4	100	8
6	F	31	2	89	10
7	F	28	3	35	8
8	M	36	6	62	24
9	M	34	3	39	3
10	M	35	2	23	4
11	M	33	6	60	18
12	F	35	3.5	107	102
13	M	23	2	35	37
14	F	36	2	125	16
15	M	48	2	49	13
16	F	36	3	38	10
17	F	29	2	120	60
18	F	32	3	67	3
19	F	35	5	76	77

[a]Mean (SD) values were as follows: age, 33.7 (5.6) years; risperidone dose, 3.1 (0.3) mg/d; basal prolactin level, 86.5 (51.9) ng/mL; final prolactin level, 40.6 (47.8) ng/mL. Abbreviations: F = female, M = male.

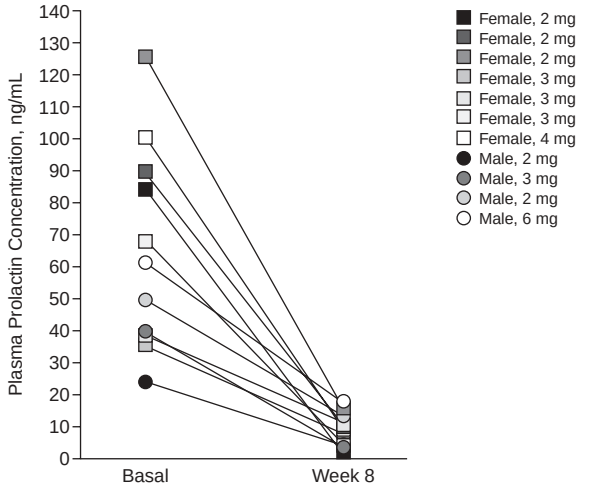
RESULTS

Table 1 shows age, sex, risperidone dose, and basal and final prolactin concentrations. At basal observation, all women reported amenorrhea and decreased libido, and 2 patients also had galactorrhea; all men reported erectile dysfunction and decreased libido.

After cabergoline treatment, prolactin concentrations were in the normal range for 11 (58%) of 19 patients (7 women, 4 men) and still pathologically increased in the remaining 8 patients (6 women, 2 men), without statistically significant differences between men and women (chi-square test). Nevertheless, the mean (SD) reduction of prolactin concentrations after cabergoline treatment was statistically significant in both groups, decreasing from 64.4 (31.7) ng/mL to 8.6 (5.9) ng/mL among patients with normalized prolactin levels ($t = 0$, $z = 2.93$, $p = .003$, Wilcoxon test for paired data) and from 116.9 (60.5) ng/mL to 84.7 (44.7) ng/mL among prolactin nonnormalized patients ($t = 3$, $z = 2.1$, $p = .036$, Wilcoxon test for paired data).

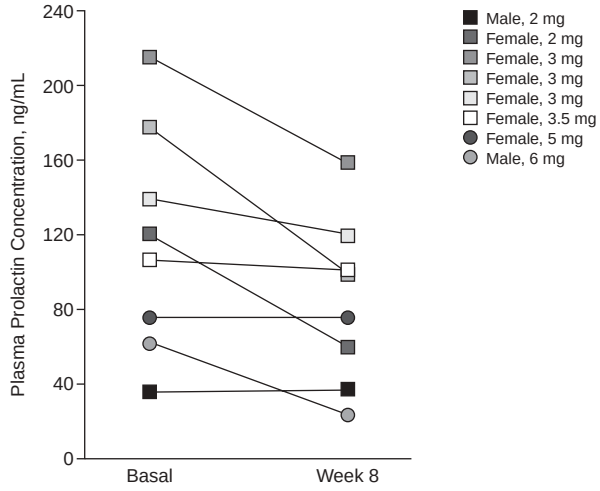
Figures 1 and 2 show change in individual plasma prolactin levels among prolactin normalized and nonnormal-

Figure 1. Plasma Prolactin Concentrations Before and After 8 Weeks of Cabergoline Treatment Among Patients With Prolactin Normalization[a]



[a]Doses listed in key refer to daily risperidone dose.

Figure 2. Plasma Prolactin Concentrations Before and After 8 Weeks of Cabergoline Treatment Among Patients Without Prolactin Normalization[a]



[a]Doses listed in key refer to daily risperidone dose.

ized patients. Normalization of prolactin values corresponded to restoration of menses, libido, and erectile function within the treatment period or within the month following cabergoline withdrawal, except for menses in 1 woman and ejaculatory dysfunction in 1 man with mixed erectile-ejaculatory symptomatology. Women with restored menses maintained cycles throughout a follow-up ranging from 2 to 3 months, and other functions restored were maintained in all patients. As expected on the basis of the final prolactin concentrations, clinical symptoms of hyperprolactinemia did not disappear in prolactin nonnormalized patients, despite the statistically significant decrease from baseline.

All responders to cabergoline were treated with the lower dose regimen of 0.125 mg/week for the entire period of study, while the patients identified at week 4 as nonresponders were treated with the higher dose of 0.125 mg twice per week beginning with the fourth week of treatment. Neither basal and final prolactin levels nor percentage of change in prolactin levels after treatment were correlated with age or risperidone dose. Nevertheless, it is worthy of note that the rate of responders to cabergoline was numerically higher among subjects with basal prolactin concentrations below the mean basal value of the whole sample (8/11) than among subjects with a basal prolactin concentration above the same value (3/8). No side effect was reported or observed, and no patient showed significant psychopathologic change, defined as a change of at least 20% in the basal total score of the Brief Psychiatric Rating Scale. During the follow-up period of 2 to 3 months after cabergoline withdrawal, psychopathologic tolerability was maintained.

DISCUSSION

The results of this pilot study showed that low-dose cabergoline was an effective and safe treatment for a significant proportion of patients with risperidone-induced hyperprolactinemia. As we hypothesized, a wide range of basal hyperprolactinemic values were reduced significantly, but a greater probability of clinical success (despite the lack of a significant response predictor) was observed among patients with low-to-medium prolactin elevations, particularly among patients with basal prolactin elevations below the sample mean basal value of 86.5 ng/mL. This result leads us to hypothesize that cabergoline treatment could be effective in most risperidone-induced hyperprolactinemia cases if we consider reference data from risperidone registration trials reporting mean plasma prolactin concentrations of up to 50 ng/mL among 377 males and females,[4] as well as some recent independent data.[15]

In nonresponders, the lack of response gives rise to some speculations. First, the most severe hyperprolactinemic responses to risperidone were a minority and might be interpreted as a kind of idiosyncratic response, rather than the simple D_2 antagonism–related effect expected in patients taking an antidopaminergic agent. Resistance to low cabergoline doses in these patients might be related to multiple effects on the tuberoinfundibular tract cells, including effects on 5-HT_2 receptors. Another explanation, concerning only the effect of D_2 receptors on prolactin release, comes from molecular biology. Two recent studies[16] found that allele 1 of a D_2 receptor gene polymorphism, Taq1, was associated with higher prolactin responsivity

among women treated with nemonapride and bromperidol. It is possible that this or other genetic features may influence prolactin responsivity to not only dopamine antagonists, but also agonists. It should be considered that our study design included doses of cabergoline that were safe for clinical use among psychotic patients and effective in most of the patients, but low in comparison to current cabergoline posology, in which doses range from 0.25 to 0.50 mg twice per week. We cannot exclude that higher doses might have normalized prolactin values in nonresponder patients, but the results should be seen in the context of the ethical priority to avoid the risk of psychopathologic iatrogenesis.

Besides the clinical effects observed, the available sample size allows very few inferences about the results obtained. Given the nature of pilot studies, with strictly clinical aims, our data should be confirmed in larger samples with longer periods of cabergoline treatment and follow-up and a more complete assessment of prolactin-related endocrinologic parameters such as estradiol and testosterone. The availability of a wider set of data could increase the probability of finding clear-cut clinical and biological response predictors.

Drug names: bromocriptine (Parlodel and others), cabergoline (Dostinex), clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

1. Wieck A, Haddad P. Hyperprolactinemia caused by antipsychotic drugs. BMJ 2002;324:250–252
2. Compton MT, Miller AH. Antipsychotic-induced hyperprolactinemia and sexual dysfunction. Psychopharmacol Bull 2002;36:143–164
3. Knegtering H, van der Moolen AEGM, Castelein S, et al. What are the effects of antipsychotics on sexual dysfunctions and endocrine functioning? Psychoneuroendocrinology 2003;28:109–123
4. Kleinberg DL, Davis JM, de Coster R, et al. Prolactin levels and adverse events in patients treated with risperidone. J Clin Psychopharmacol 1999;19:57–61
5. Ryan MCM, Thakore JH. Physical consequences of schizophrenia and its treatment: the metabolic syndrome. Life Sci 2002;71:239–257
6. Koro CE, Fedder DO, L'Italien GJ, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case control study. BMJ 2002;325:1–5
7. Nasrallah HA, Tandon R. Efficacy, safety, and tolerability of quetiapine in patients with schizophrenia. J Clin Psychiatry 2002;63(suppl 13):12–20
8. Alexiadis M, Whitehorn D, Woodley H, et al. Prolactin elevation with quetiapine [letter]. Am J Psychiatry 2002;159:1608–1609
9. Keller R, Mongini F. Switch to quetiapine in antipsychotic agent-related hyperprolactinemia. Neurol Sci 2002;23:233–235
10. Webster J, Piscitelli G, Polli A, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. N Engl J Med 1994;331:904–909
11. Tollin SR. Use of the dopamine agonists bromocriptine and cabergoline in the management of risperidone-induced hyperprolactinemia in patients with psychotic disorders. J Endocrinol Invest 2000;23:765–770
12. Cohen LG, Biederman J. Treatment of risperidone-induced hyperprolactinemia with a dopamine agonist in children. J Child Adolesc Psychopharmacol 2001;11:435–440
13. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: A New Comprehensive Rating Scale for Psychotropic Drugs and a Cross-Sectional Study of Side Effects in Neuroleptic-Treated Patients. Acta Psychiatr Scand Suppl 1987;334:1–100
14. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
15. Kinon BJ, Gilmore JA, Liu H, et al. Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. Psychoneuroendocrinology 2003;28:55–68
16. Mihara K, Suzuki A, Kondo T, et al. Relationship between Taq1 A dopamine D2 receptor (DRD2) polymorphism and prolactin response to bromperidol. Am J Med Genet 2001;105:271–274