Low-dose risperidone augmentation of antidepressants or anxiolytics is associated with hyperprolactinemia

Miloslav Kopecek, Martin Bares, Jiri Horacek & Pavel Mohr

Prague Psychiatric Centre, 3rd Medical Faculty Prague – Charles University, Centre of Neuropsychiatric Studies in Prague, Prague, Czech Republic

Correspondence to: Miloslav Kopecek, MD
Prague Psychiatric Centre,
Ústavní 91, Prague 8 – Bohnice, Czech Republic
PHONE/FAX: +420-22663361
EMAIL: kopecek@pcp.lf3.cuni.cz

Submitted: August 18, 2006 *Accepted: September 10, 2006*

Key words: **risperidone; prolactinemia; depression; anxiety; side effect; endocrinology**

Neuroendocrinol Lett 2006; **27**(6):803–806 **PMID:** 17187006 NEL270606A21 **www.nel.edu**

Abstract

OBJECTIVE: Risperidone in antipsychotic doses induces hyperprolactinemia. The aim of this study was to verify whether the same is true for low doses of risperidone (0.5–2 mg per day) added to antidepressants or anxiolytics.

METHODS: Prolactin levels were measured in 4 men (mean age 49.5±19.1 years) and 8 women (mean age 31.3±8.2 years) inpatients with depressive and anxiety disorders who were treated with risperidone (median doses per day 1.25 mg) for median 15.5 days as an augmentation treatment to antidepressants (n=8), anxiolytics (n=6) and mood stabilizers (n=2).

RESULTS: 11 of 12 patients had hyperprolactinemia. Median plasma prolactin level was 1598 mIU/ml, 95% CI 1 040–2 661 mIU/ml. Significant correlation between risperidone daily dose and plasma prolactin level (Spearman's R=0.655, p=0.02) was detected. Two women suffered from galactorrhea and one from amenorrhea.

CONCLUSIONS: Even low doses of risperidone used as an augmentation to antidepressants or benzodiazepines are associated with hyperprolactinemia and can induce endocrinological side effects. The co-medication of antidepressants and benzodiazepines can potentially increase intensity of prolactinemia.

Abbreviations and units

mIU/ml	- milli-International Units per milliliter
EPS	- extrapyramidal syndrome
SRI	- serotonin reuptake inhibitor
OCD	- Obsessive compulsive disorder
mg	- milligram
S.D.	- standard deviation
ICD-10	- International Classification of Diseases – 10th Revision
TSH	- Thyroid-Stimulating Hormone
T4	- thyroxine
CMIA	- Chemiluminiscent Microparticle Immunoassay
c.v.	- coefficients of variation
mIU/l	- milli-International Units per liter
nmol/l	- nanomol per liter

Introduction

Risperidone is a benzisoxazole antipsychotic which blocks with high selectivity dopamine D2 and serotonin 5-HT2a receptors. Suggested minimal effective dose of risperidone based on PET-measures of dopamine D2 receptor occupancy in schizophrenia patients is 4 mg [12]. The doses higher than 6 mg represent a greater risk for EPS induction [16]. Recent studies showed that low doses of risperidone (0.5–2 mg) could be used to augment response of serotonin reuptake inhibitors (SRIs) in patients with OCD [9,11], enhance response of antidepres-

ORIGINAL ARTICLE

sants in patients with generalized anxiety disorder [2], post-traumatic stress disorder [1,6,10] or depression [13,15]. Risperidone, similarly to amisulpride, have a greater propensity to induce prolactin elevation than other newer antipsychotics [5,8]. A recent study showed that low-dose risperidone (0.75–2 mg/day, mean ±S.D. dose 1.26±0.42) lead in children with autistic disorder to the significant increase of serum prolactin levels after 12 weeks of treatment [4]. However, no data have been so far published on the endocrinological side effects of low-dose risperidone (≤2 mg) used as an add-on therapy of depressive or anxiety disorders in adults. The aim of our study was to investigate effects of low dose of risperidone (0.5–2 mg per day) used as augmentation therapy of depressive or anxiety disorders on prolactin plasma levels.

Methods

Study protocol was approved by the Ethical Committee of the Prague Psychiatric Center, informed consent was obtained from all participants. Study subjects were inpatients with depressive or anxiety disorders diagnosed according to the ICD-10 criteria. Prolactin levels were assessed in 12 patients (4 men, 8 women) who were treated with 0.5–2 mg of risperidone per day (median 1.25 mg) as an augmentation treatment to antidepressants (n=8), anxiolytics (n=6) or mood stabilizers (n=2). The patients used risperidone for median of 15.5 days (1st quartile 8.5 days, 3rd quartile 91.5 days). All of them had biochemical assessment and thyroidal screening (plasma level of Thyroid-Stimulating Hormone – TSH or total thyroxine plasma level – T4) to rule out other physical conditions that may affect prolactin level such as primary hypothyroidism, adrenal insufficiency, renal failure, hepatic insufficiency, or pregnancy. The clinical characteristics of our sample are summarized in Table 1. The mean age was 31.3±8.2 years in women and 49.5±19.1 years in men. No patient used any other compound capable of blocking dopamine D2 receptors, except for risperidone. The blood samples were always taken at 6:00 a.m. (minimally 8 hours after last dose of risperidone) and then centrifuged to separate serum. Prolactin levels were

Table 1. Clinical characteristics of patients.

Sex	Age (years)	Diagnosis (ICD-10)	Dose of risperidone (mg/day)	Duration of risperidone therapy (days)	Prolactin plasma level (mIU/ml)	TSH (mIU/l), T4 (nmol/l)	Side effects	Concomitant medication (mg/day)	
M	63	F 33.1	1	7	505*	0.9, 76.6	no	venlafaxine bromazepam	150 9
M	18	F 42.2	1.5	186	1318*	X, 82.9	no	sertraline	100
M	50	F 33.1	1	9	541*	0.51, 118	no	venlafaxine alprazolam	150 3
M	49	F 32.2	1	180	268	2.27, 49.7†	no	sertraline dibenzepine	200 240
F	21	F 31.3	2	62	3082* 43+	2.79, 70.7	musclerigidity amenorrhea	valproate clonazepam	1500 1.5
F	17	F 43.1	0.5	21	887*	3.26, 133.5	no	seropram	20
F	36	F 33.1 F 41.2	2	14	2368*	3.01, 76.9	galactorrhea	venlafaxine amitriptyline alprazolam hydroxyzine	150 50 2.5 50
F	39	F 43.2	2	17	2322*	2.55, 99.9	no	hydroxyzine alprazolam	150 2.75
F	30	F60.4	1.5	6	1865*	4.7*, 113.3	no	clonazepam lamotrigine	1 100
F	38	F 41.1	1	10	1331*	2.6, 88.8	no	no	
F	33	F 42.2	1	608	3467*	0.43, 110.6	no	clomipramine	225
F	37	F 41.2	2	7	4250* 1080++	2.42, 67.1	galactorrhea	escitalopram	20

Legend: M – male, F – female, *increased plasma level, †decreased plasma level, X not assessed, + prolactin plasma level during olanzapine augmentation, ++ prolactin plasma level during quetiapine augmentation. F32.2 Severe Depressive Episode Without Psychotic Symptoms, F33.1 Recurrent Depressive Disorder with Current Moderate Symptoms, F 31.3, F 41.1 Panic Disorder, F 41.2 Mixed Anxiety Depression, F 60.31 Borderline Personality Disorder, F 42.2 Obsessive compulsive disorder, F 43.1 Post-Traumatic Stress Disorder, F 43.2 Adjustment Disorder - Depressive Type.

determined by the Chemiluminiscent Microparticle Immunoassay (CMIA). The sensitivity of the assay is 12.6 mIU/ml (intra-assay coefficients of variation [c.v.]: 3.8%, inter-assay c.v. 4.7%). The normal range established for this assay is within 54–381 mIU/ml for men and 25–513 mIU/ml for women. Due to the sample size, the non-parametric statistical tests, Mann-Whitney U Test and Spearman Rank Order Correlations Test, were used.

Results

Eleven of twelve patients had hyperprolactinemia (plasma prolactin level over 381 mIU/ml for men and 513 mIU/ml for women). Median plasma prolactin level was 1598 mIU/ml, 95% Confidence interval (1 040–2 661 mIU/ml). The prolactin levels were significantly higher in women (median 2 345 mIU/ml; 1st quartile 1 598 mIU/ml, 3rd quartile 3 274 mIU/ml) than men (median 523 mIU/ml; 1st quartile 386 mIU/ml, 3rd quartile 929 mIU/ml; Mann-Whitney U Test, Z=2.54, exact p=0.008). No statistically significant gender difference was detected in age, mean risperidone daily dose, or duration of treatment. We found a significant correlation between risperidone daily doses and plasma prolactin levels (Spearman's Rank Order Correlations R=0.655, Z=2.74, p=0.02). Two women reported galactorrhea and other woman suffered from amenorrhea and muscle rigidity (Table 1). Two of them were reassessed after switch to 10 mg of olanzapine or 300 mg of quetiapine, respectively. In both patients, decreased prolactin plasma levels (Table 1) with subsequent disappearance of muscle rigidity, amenorrhea and galactorrhea were observed.

Discussion

We detected hyperprolactinemia in 92% of patients with depressive or anxiety disorders treated with low dose of risperidone as an augmentation of antidepressants, benzodiazepines, mood stabilizers, or in monotherapy. Moreover, in three patients with hyperprolactinemia secondary amenorrhea or galactorrhea were observed. Except for two patients with positive thyroid screening test indicating possibility of hypothyroidism, no other patients had other physical condition known to affect prolactin level. One patient with positive thyroid screening test had normal plasma prolactin level, the second had hyperprolactinemia. We observed decrease of prolactin levels and disappearance of muscle rigidity, amenorrhea and galactorrhea in two patients with symptomatic hyperprolactinemia after the switch to olanzapine and quetiapine.

Our results are in agreement with an animal study that found the dissociation between central (striatal) and peripheral (pituitary) dopamine D2 receptor effects following risperidone administration [7]. In risperidone, the dissociation results in a lower occupancy of D2 receptors in the striatum and higher occupancy in the pituitary [7]. In our study the high occupancy in the pituitary lead to hyperprolactinemia in 11 patients but only one of them suffered from EPS. The fact that even low dose of risperidone can induce hyperprolactinemia and positive correlation between risperidone doses and plasma prolactin levels suggest that there is no threshold for hyperprolactinemia in doses over 0.5 mg per day and that 5HT2a antagonism does not protect from prolactin elevation.

There are several caveats to our findings. First, we have no information on prolactin plasma levels before risperidone therapy so we can not completely rule out possibility of pre-existing hyperprolactinemia. Although no physical condition that could affect prolactin level was detected in 11 patients, six patients were treated with tricyclic antidepressants or SRIs, which have been reported to increase prolactin secretion [3,14]. On the other hand, in 13 single case reports describing nonpuerperal lactation associated with the use of SRIs in women, no patient displayed plasma prolactin levels above 1 800 mIU/ml [3]. Second, we can not rule out potential pharmacodynamic interactions between antidepressants, anxiolytics or mood stabilizers and risperidone but we can exclude the role of pharmacokinetic interactions between them. Risperidone is metabolized via cytochrome P450 enzyme 2D6 and co-administration of CYP4502D6 inhibitors can increase risperidone plasma levels. Our patients were treated with drugs that have no influence on CYP4502D6 inhibition (alprazolam, buspirone, clonazepam, clomipramine, diazepam, lamotrigine, valproate) or are very weak CYP4502D6 inhibitors (citalopram, venlafaxine). Third caveat to our study findings is a rather small sample size.

Even with the acknowledgment of the discussed limitations we believe that our results have clinical consequences. Prolactin plasma levels were markedly high especially in females (Table 1). Long-lasting hyperprolactinemia can potentionally cause such severe endocrinological side effects as gynecomastia, feeling of engorgement, galactorrhea, infertility (anovulatory cycles), menstrual irregularity (oligomenorrhea, amenorrhea), sexual dysfunction (decreased libido, impaired arousal, erectile or ejaculatory dysfunction, impaired orgasm, impaired spermatogenesis, azoospermia, dyspareunia), acne and hirsutism in women (due to relative androgen excess compared to low estrogen levels) and increased long-term risk of osteoporosis [5]. It is necessary to be aware that these side effects which are usually observed in the first generation antipsychotics, can be associated even with the low dose risperidone monotherapy or as an add-on medication to antidepressants, benzodiazepines, or mood stabilizers.

With the more extensive use of risperidone, especially in other indications beyond schizohrenia and psychotic disorders, risperidone-induced hyperprolactinemia could become an increasingly common and potentially clinically significant syndrome. The presence of symptoms of hyperprolactinemia should be assessed prior onset of risperidone treatment and monitored regularly thereafter.

Conclusion

Even low doses of risperidone used either as an augmentation of treatment with antidepressants, benzodiazepines, mood stabilizers or as a monotherapy can be associated with hyperprolactinemia. The psychiatrists should keep in mind the subsequent clinically relevant endocrinological side effects.

Acknowledgements

This work was supported by the research project MSM 0021620816 from Ministry of Education, Youth and Sports, the Czech Republic.

REFERENCES

1 Bartzokis G, Lu PH, Turner J, Mintz J, Saunders CS: Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. Biol Psychiatry. 2005; **57**:474–9.
2 Brawman-Mintzer O, Knapp RG, Nietert PJ: Adjunctive risperidone in generalized anxiety disorder: a double-blind, placebo-controlled study. J Clin Psychiatry. 2005; **66**:1321–5.
3 Emiliano AB, Fudge JL. From galactorrhea to osteopenia: rethinking serotonin-prolactin interactions. Neuropsychopharmacology. 2004; **29**(5):833–46.
4 Gagliano A, Germano E, Pustorino G, Impallomeni C, D'Arrigo C, Calamoneri F, Spina E: Risperidone treatment of children with autistic disorder: effectiveness, tolerability, and pharmacokinetic implications. J Child Adolesc Psychopharmacol. 2004; **14**:39–47.
5 Haddad PM, Wieck A: Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. Drugs. 2004; **64**:2291–314.
6 Hamner MB, Faldowski RA, Ulmer HG, Frueh BC, Huber MG, Arana GW: Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. Int Clin Psychopharmacol. 2003; **18**:1–8.
7 Kapur S, Langlois X, Vinken P, Megens AA, De CR, Andrews JS: The differential effects of atypical antipsychotics on prolactin elevation are explained by their differential blood-brain disposition: a pharmacological analysis in rats. J Pharmacol Exp Ther. 2002; **302**:1129–34.
8 Kopecek M, Bares M, Svarc J, Dockery C, Horacek J: Hyperprolactinemia after low dose of amisulpride. Neuro Endocrinol Lett. 2004; **25**:419–22.
9 Li X, May RS, Tolbert LC, Jackson WT, Flournoy JM, Baxter LR: Risperidone and haloperidol augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder: a crossover study. J Clin Psychiatry. 2005; **66**:736–43.
10 Monnelly EP, Ciraulo DA, Knapp C, Keane T: Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. J Clin Psychopharmacol. 2003; **23**:193–6.
11 McDougle CJ, Epperson CN, Pelton GH, Wasylink S, Price LH: A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry. 2000; **57**:794–801.
12 Nyberg S, Eriksson B, Oxenstierna G, Halldin C, Farde L: Suggested minimal effective dose of risperidone based on PET-measured D2 and 5-HT2A receptor occupancy in schizophrenic patients. Am J Psychiatry. 1999; **156**:869–875.
13 Ostroff RB, Nelson JC: Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. J Clin Psychiatry. 1999; **60**:256–259.
14 Papakostas GI, Miller KK, Petersen T, Sklarsky KG, Hilliker SE, Klibanski A, Fava M. Serum Prolactin Levels Among Outpatients With Major Depressive Disorder During the Acute Phase of Treatment With Fluoxetine. J Clin Psychiatry. 2006; **67**(6):952–7.
15 Sharpley AL, Bhagwagar Z, Hafizi S, Whale WR, Gijsman HJ, Cowen PJ: Risperidone augmentation decreases rapid eye movement sleep and decreases wake in treatment-resistant depressed patients. J Clin Psychiatry. 2003; **64**:192–6.
16 Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. CNS Drugs. 2002; **16**:23–45.