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

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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.

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 antidepressant...
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.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis (ICD-10)</th>
<th>Dose of risperidone (mg/day)</th>
<th>Duration of risperidone therapy (days)</th>
<th>Prolactin plasma level (mIU/ml)</th>
<th>TSH (mIU/l), T4 (nmol/l)</th>
<th>Side effects</th>
<th>Concomitant medication (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>63</td>
<td>F 33.1</td>
<td>1</td>
<td>7</td>
<td>505*</td>
<td>0.9, 76.6</td>
<td>no</td>
<td>venlafaxine</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>F 42.2</td>
<td>1.5</td>
<td>186</td>
<td>1318*</td>
<td>X, 82.9</td>
<td>no</td>
<td>sertraline</td>
</tr>
<tr>
<td>M</td>
<td>50</td>
<td>F 33.1</td>
<td>1</td>
<td>9</td>
<td>541*</td>
<td>0.51, 118</td>
<td>no</td>
<td>venlafaxine</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>F 32.2</td>
<td>1</td>
<td>180</td>
<td>268</td>
<td>2.27, 49.1†</td>
<td>no</td>
<td>sertraline, dibenepine</td>
</tr>
<tr>
<td>F</td>
<td>21</td>
<td>F 31.3</td>
<td>2</td>
<td>62</td>
<td>3082*</td>
<td>2.79, 70.7</td>
<td>musclerigidity, amenorrhea</td>
<td>valproate, clonazepam</td>
</tr>
<tr>
<td>F</td>
<td>17</td>
<td>F 43.1</td>
<td>0.5</td>
<td>21</td>
<td>887*</td>
<td>3.26, 133.5</td>
<td>no</td>
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<tr>
<td>F</td>
<td>36</td>
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<td>2</td>
<td>14</td>
<td>2368*</td>
<td>3.01, 76.9</td>
<td>galactorrhea</td>
<td>venlafaxine, amitriptyline, alprazolam, hydroxyzine</td>
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<tr>
<td></td>
<td>39</td>
<td>F 43.2</td>
<td>2</td>
<td>17</td>
<td>2322*</td>
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<td>no</td>
<td>hydroxyzine, alprazolam</td>
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<tr>
<td>F</td>
<td>30</td>
<td>F 60.4</td>
<td>1.5</td>
<td>6</td>
<td>1865*</td>
<td>4.7*, 113.3</td>
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<td>clonazepam, lamotrigine</td>
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<tr>
<td>F</td>
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<td>F 41.1</td>
<td>1</td>
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<tr>
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<td>1</td>
<td>608</td>
<td>3467*</td>
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<td>no</td>
<td>clomipramine, escitalopram</td>
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<tr>
<td>F</td>
<td>37</td>
<td>F 41.2</td>
<td>2</td>
<td>7</td>
<td>4250*</td>
<td>2.42, 67.1</td>
<td>galactorrhea</td>
<td>escitalopram</td>
</tr>
</tbody>
</table>

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 513–381 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 (1040–2661 mIU/ml). The prolactin levels were significantly higher in women (median 2345 mIU/ml; 1st quartile 1598 mIU/ml, 3rd quartile 3274 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 nonpupetal lactication associated with the use of SRIs in women, no patient displayed plasma prolactin levels above 1800 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 (oligomenorrhoea, amenorrhoea), sexual dysfunction (decreased libido, impaired arousal, erectile or ejaculatory dysfunction, impared 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 schizophrenia 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.

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REFERENCES

16 Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. CNS Drugs. 2002; 16:23–45.