Prolactin level during 5 years of risperidone treatment in patients with psychotic disorders.

Eberhard, Jonas; Lindström, E; Holstad, M.; Levander, Sten

Published in: 
Acta Psychiatrica Scandinavica

DOI: 
10.1111/j.1600-0447.2006.00897.x

Published: 2007-01-01

Citation for published version (APA):
Prolactin level during 5 years of risperidone treatment in patients with psychotic disorders

Eberhard J, Lindström E, Holstad M, Levander S. Prolactin level during 5 years of risperidone treatment in patients with psychotic disorders.

Objective: To investigate prolactin levels and related side effects in 128 men and 90 women initially treated with risperidone.

Method: Patients initially treated with risperidone were followed over 5 years, during which 45% were switched to other antipsychotic drugs.

Results: Initially, prolactin levels were fivefold the norm in women, and threefold in men. Diagnosis did not affect the prolactin level if adjustment for sex, current age, and age at onset of psychosis was applied. Prolactin levels did not correlate significantly neither with any Positive and Negative Symptom Scale item or subscale, nor with side effects. Drugs other than risperidone were not associated with high prolactin levels. For patients on continuous monotherapy risperidone treatment, there was a marked linear reduction of prolactin level over all 5 years.

Conclusion: Risperidone induces a higher prolactin elevation than other atypical antipsychotics, but the effect adapts over time. Prolactin was not associated with expected side effects (e.g. sexual, mental, or weight gain).

Significant outcomes

- Risperidone was the only drug associated with high prolactin levels.
- The data suggest the prolactin release to be associated with the active metabolite 9-OH-risperidone, and not with the mother substance.
- For the patients remaining on risperidone there was a significant linear reduction of prolactin level over the 5 years of the study.

Limitations

- Wide inclusion criteria and presumably substantial patient heterogeneity.
- Naturalistic multi-center design with high drop-out, particularly the first year.
- Much larger sample size of risperidone treated patients vs. comparators.

Introduction

Antipsychotic drugs have been one of the cornerstones in the treatment of schizophrenia and many other psychotic disorders for more than 50 years. All current antipsychotic drugs have the power to modulate dopamine D2-mediated transmission. The antipsychotic effect is assumed to be exerted through interference with the dopaminergic neurons of the mesolimbic system (1, 2). Dopamine D2
receptors are not confined to the mesolimbic structures, neither is that structure and receptor population exclusively linked with the symptoms and functional problems that characterize psychotic disorders. Therefore, D2 antagonists generate unwanted side effects, and are effective only for some of the manifestations of such disorders. Consequently, the search for new antipsychotics has continued over the 50 years since chlorpromazine was introduced (3).

Risperidone entered clinical trials in the early 1990s and is now a commonly used 'atypical' antipsychotic compound with a high affinity for dopamine D2 and serotonin 5-HT2 receptors. Many studies suggest that risperidone is effective in the treatment of both positive, negative and affective symptoms in schizophrenia, and that the frequency of extrapyramidal side effects is lower than for 'typical' ones (4–8). However, even if risperidone is regarded as an atypical antipsychotic it gives rise to a substantial increase of serum-prolactin during treatment, both short- and long-term (9).

Prolactin was discovered more than 60 years ago as a growth-stimulating hormone normally associated with lactation. However, it has also been suggested to play a role in many other biological functions such as reproduction, glucose metabolism and in regulation of the immune system (10). Over 200 biological functions have been associated with prolactin which once lead to a proposal that prolactin should be renamed 'versatilin' or 'omnipotin' (11).

The factors regulating prolactin secretion have been explored in detail by Öhman and Axelsson (12). The secretion of prolactin from the anterior lobe of the pituitary is under tonic stimulation by the hypothalamus. Dopamine, released from neurons is an inhibitory factor on secretion of prolactin. Once typical antipsychotics block dopamine receptors, there is a rise in serum-prolactin. The prolactin response may perhaps reflect the efficacy of the dopamine response blockade in the tubero-infundibular system and therefore potentially also mirror the antipsychotic effect exerted in other brain structures. Conventional antipsychotics, particularly the high-dose ones, and one of the atypicals, risperidone (13), may cause significant elevations in prolactin. It has been suggested that it is the 9-OH-metabolite, which plays the predominant role in risperidone’s effect on the prolactin release (14). Clozapine, olanzapine, and ziprasidone give rise to minimal elevations, which may be due to a higher 5-HT2A/D2 occupancy and differential effects on dopamine transmission with less interference in the tubero-infundibular pathway.

An exceptional older 'typical' antipsychotic is Melperone, which does not increase prolactin levels, nor cause EPS, thereby suggesting 'atypicality' (15).

Dose-related hyperprolactinaemia is prevalent among both women and men treated with conventional antipsychotics or risperidone (16). Switching to a prolactin-sparing antipsychotic results in normalization of the prolactin level (17). It is important to consider clinical correlates of hyperprolactinaemia in more detail when selecting treatment – it has been suggested that hyperprolactinaemia may be associated both with sexual and/or other side effects, and even with beneficial effects, such as an additional antipsychotic effect. However, in these respects the literature is sparse and inconsistent, particularly for long-term effects. Some effects often assumed to be linked to a prolactin increase, may well be linked to other aspects of the disease, rather than the medication. In a recent study by Hummer et al. (18) an assumed relationship between osteoporosis and prolactin-increasing antipsychotics could not be corroborated, except and maybe for men and one anatomical structure (mineral loss in the lumbar region).

**Aims of the study**

The main aim of the present study was to investigate the effects of risperidone, 9-OH-risperidone, and other antipsychotic compounds on prolactin levels, and the associations between prolactin level and symptoms, as well as certain side effects assumed to be prolactin-related (sexual dysfunction, mental side effects, and weight gain). Other pharmacokinetic and pharmacodynamic effects of risperidone were also investigated.

**Material and methods**

The patients in this longitudinal, national, multi-center Phase IV-trial were examined annually during 5 years. Patients gave written informed consent and the study was approved by local ethics committees. At inclusion (year 0) selected patients \(N = 225\) were all treated with risperidone during maintenance treatment. Some of the patients had additional psychotropic medication, i.e. other antipsychotics, benzodiazepines, lithium, anticholinergics, or antidepressants. At the day of inclusion and at the day of the following yearly investigations (year 1 to year 5), information was collected according to a comprehensive study protocol.
Laboratory tests

Blood samples were drawn at steady-state, between 7 and 9 AM, before the first antipsychotic dose of the day (approximately 12 h after the last intake of drug). The serum concentrations of risperidone and 9-OH-risperidone were determined by use of high-pressure liquid chromatography. The serum concentration of prolactin was measured by a radio immuno-chemical assay (19). The individual increase in prolactin level relative norms was calculated from the laboratory’s upper normal reference values (300 and 500 nmol/l for men and women respectively).

Prolactin levels and type and dose of antipsychotic drugs at study entry

A majority (181) of the 218 risperidone-treated patients were on risperidone monotherapy. Seven had another atypical drug, and 30 had one or several conventional antipsychotics (20). Chlorpromazine (CPZ) equivalent doses were calculated and no significant correlations between prolactin level and any of the CPZ variables, or drug types were found. Unfortunately, there was no information about the drug history of the patients prior to study entry (1 month or more backwards, cf. 20).

Instruments

Side effects. The ‘Udvalg for Kliniske Undersøgelser’ (Danish for ‘Choice of clinical examinations’) – UKU side effect scale (21) is a comprehensive instrument for use in clinical drug trials and routine clinical practice. It comprises ratings (0–4) of 48 single items, clustered into four categories: Mental, Neurological, Autonomic, and Other side effects. The UKU was used in order to evaluate mental side effects (10 items) and sexual side effects (including gynecomastia and galactorrhea) which are listed under other side effects: two for men (erectile dysfunction and ejaculatory dysfunction), three for women (dry vagina, amenorrhea, and menorrhagia) and five sex-independent ones (increased or reduced sexual desire, orgasmic dysfunction, gynecomastia, galactorrhea). The sexual side effects were analyzed on item level. The scores of the 10 mental side effects were summed to a total score.

Weight and BMI. Weight and height were measured by analogue scales and wall-mounted stadiometers at baseline and weight at each follow-up. Body mass index (BMI; kg/m²) was calculated as the Quetelet’s index (weight/height²). Subjects were classified as overweight (BMI > 25 kg/m²) and obese (BMI > 30 kg/m²). A detailed analysis of the weight data is presented in Neovius et al. (22).

Analyses of study entry data. The way that the analyses of side effects in relation to prolactin levels were chosen were based on the following lines of reasoning. The study entry session involved more patients than the other sessions, and all were treated with risperidone since at least 1 month. This time period is not enough for changes in weight to occur. Furthermore, weight/BMI is determined by a multitude of factors, which are irrelevant in the present context. Thus, these analyses must be based on changes in weight over a year in relation to the prolactin level of these years. In contrast, sexual and mental side effects according to the UKU instrument are best analysed for study entry data, but parallel changes in side effects and prolactin data may also be of some interest because in the year 1 to year 5 sessions many patients were switched to other antipsychotic drugs and some became drug-free.

Statistical methods

Standard statistical analysis methods were used as specified in the text. Calculations were performed using spss 12.0. Prolactin values were skewed – a logarithmic transformation yielded approximately normal distributions. All parametric statistics involving prolactin level calculations are based on log-transformed data, antilogged in the tables.

Results

Patients

In 218 of the 225 risperidone-treated patients prolactin data were obtained, which are analysed in this report. The clinical characteristics at study entry, including Positive and Negative Symptom Scale (PANSS; 23) scores, are given in Table 1. According to their DSM-IV diagnosis the patients were divided into five diagnostic groups: schizophrenia, schizoaf/...
Prolactin levels over time

Fifty-nine patients had complete data over the 5 years (i.e. six, or in a few cases five separate assessments). Mean prolactin levels over the six assessments are shown in Table 2. The levels dropped significantly from the first session until the last, but more slowly from the third as evidenced by an ANOVA for repeated measures with polynomial decomposition. There was a highly significant linear trend ($F(1, 58) = 74.8, P << 0.001$), and a significant quadratic trend ($F(1, 58) = 12.7, P < 0.001$). The intra-class correlation coefficient was very high ($r = 0.92$, corresponding to a single measure correlation of 0.67).

For 20 patients on continuous risperidone monotherapy over the 5 years, there was a highly significant linear reduction of prolactin level over all years ($F(1, 19) = 25.1, P < 0.001$) – no other polynomial decomposition factor was significant, and there was no relation to CPZ level.

An analysis of shifts of drugs over the 5 years yielded the following results. At study entry, 37 patients had another antipsychotic drug, in addition to risperidone. There was no significant difference in prolactin level. At study end, a total of 295 pairs of consecutive years were available for analysis (i.e. year 0 vs. year 1, year 1 vs. year 2, etc.). Preliminary analyses showed clearly that one drug alone was associated with prolactin increase: risperidone. Therefore, the different drugs were collapsed into three categories: no drug, risperidone, and all other drugs. Over the 295 year-pairs there were eight different drug combinations (Table 3). An ANOVA for repeated measures (year 1 and 2) including drug combination and sex yielded two significant main effects ($P < 0.001$), of drug combination and sex. Inspection of the means (Table 3) verifies that risperidone is the only drug that is associated with high prolactin levels – the other drugs do not differ from the ‘NoDrug’ condition. The cross-tabulation also suggests differential drug treatment strategies for the sexes ($X^2(8) = 27.6, P < 0.001$). Women tended to remain on risperidone. Men tended to remain on

---

**Table 2.** Prolactin level (nmol/l) for 59 subjects over 5 years, and concurrently sum of CPZ equivalent doses for all antipsychotic drugs and for risperidone separately

<table>
<thead>
<tr>
<th>Year</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin level (nmol/l)</td>
<td>1192</td>
<td>730</td>
<td>533</td>
<td>543</td>
<td>396</td>
<td>412</td>
</tr>
<tr>
<td>CP2 total</td>
<td>264 ± 134</td>
<td>239 ± 137</td>
<td>263 ± 196</td>
<td>303 ± 231</td>
<td>273 ± 180</td>
<td>268 ± 216</td>
</tr>
<tr>
<td>CP2 risp</td>
<td>232 ± 131</td>
<td>142 ± 140</td>
<td>131 ± 158</td>
<td>137 ± 161</td>
<td>130 ± 159</td>
<td>119 ± 159</td>
</tr>
</tbody>
</table>

**Table 3.** Prolactin levels for consecutive pairs of years classified according to drug combination

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (M/W)</td>
<td>Women (M/W)</td>
</tr>
<tr>
<td>No-drug–No drug</td>
<td>332 ± 61</td>
<td>508 ± 129</td>
</tr>
<tr>
<td>Risper–Risper</td>
<td>832 ± 79</td>
<td>1295 ± 117</td>
</tr>
<tr>
<td>Other–Other</td>
<td>197 ± 21</td>
<td>374 ± 90</td>
</tr>
<tr>
<td>No-drug–Risper</td>
<td>401 ± 180</td>
<td>2116 ± 1185</td>
</tr>
<tr>
<td>No-drug–Other</td>
<td>103 ± 29</td>
<td>72 ± 129</td>
</tr>
<tr>
<td>Risper–No drug</td>
<td>556 ± 215</td>
<td>246 ± 97</td>
</tr>
<tr>
<td>Other–No drug</td>
<td>161 ± 90</td>
<td>210 ± 95</td>
</tr>
<tr>
<td>Other–Risper</td>
<td>275 ± 124</td>
<td>1042 ± 480</td>
</tr>
</tbody>
</table>

---

Prolactin during 5 years of risperidone treatment

($F = 12.7, P < 0.001$). The intra-class correlation coefficient was very high ($r = 0.92$, corresponding to a single measure correlation of 0.67).

**PANSS:** Positive, Negative, Disorganisation, Affective.
other drugs than risperidone, and were more often drug-free.

Prolactin levels and plasma levels of risperidone and 9-OH-risperidone

Given the finding that risperidone is strongly associated with prolactin increase, it is of some interest to assess the contribution to this effect of the mother substance and its active metabolite, 9-OH-risperidone. The first 2 years provided enough data to analyze the differential association between prolactin increase and the plasma levels of risperidone and its metabolite (Table 4). The two sexes are analyzed separately. The plasma levels of the two compounds did not differ between the sexes. All four correlations between prolactin and 9-OH-risperidone plasma levels were significant – none was significant for the mother substance. Thus, the prolactin increase associated with risperidone treatment appears to be associated with its main and active metabolite, 9-OH-risperidone, which has previously been suggested by Knegtering et al. (14).

Discussion

The main finding of this 5-year longitudinal study of prolactin levels was that risperidone but not the other antipsychotics was strongly associated with high prolactin levels. This increase was more pronounced in women. There was a substantial reduction of prolactin levels over all 5 years during monotherapy with risperidone. The prolactin increase was associated with the plasma level of the main metabolite (9-OH-risperidone) rather than with the mother substance. Few other clinical effects of an increase in prolactin level could be identified. In particular, there was no association between high prolactin levels and sexual side effects.

In the present study all patients were treated with risperidone at inclusion. After 5 years approximately 25% of the patients had been switched to olanzapine or clozapine. Other patients, approximately 15%, were treated with conventional antipsychotics (high- as well as low-dose ones) as the main antipsychotic drug, and a small group of patients, around 12% were drug-free. The different medication histories of the patients over the 5 years influence prolactin levels when the whole group is analyzed. All patients had risperidone at study entry, and had high prolactin levels at that point in time. Prolactin levels appeared to drop over time by two mechanisms – switch to other compounds or termination of drug treatment, and adaptation to the continuous treatment with antipsychotic compounds. This adaptation was substantially slower for risperidone than for the other active compounds but continued linearly over the full 5-year period. The study did not have enough statistical power to separate the other compounds from each other or even from the drug-free condition. The findings are consistent with previous studies suggesting that the effects on prolactin levels of typical and atypical antipsychotics are graded in relation to dose and duration of the drug treatment, reflecting the different binding
Properties of each drug on tubero-infundibular dopamine D2 receptors (24, 25) as well as adaptation (up- or down-regulation of receptors). Sulpiride and amisulpride known to act primarily as D2 antagonists (and thereby suspected to stimulate prolactin secretion) are not registered in Sweden, and thus were not used in this study.

Zhang et al. (26) explored the effect of risperidone on serum prolactin and the relationship between change in prolactin level and therapeutic outcome in 30 male inpatients during 12 weeks of treatment with risperidone in a fixed dose of 6 mg/day. They found that risperidone treatment significantly increased the serum prolactin levels, and that there was a positive and significant relationship between the change in prolactin from pre- to post-treatment and the reduction rate of PANSS positive subscores. The serum prolactin levels at baseline could be used to predict the responses of schizophrenic patients to risperidone. As previously described by Öhman and Axelsson (12), the present study confirmed that the prolactin increase was more pronounced in women than in men (five vs. three times the norm values, respectively), in spite of the fact that women received a lower dose of antipsychotic drug. However, they did not differ in terms of plasma levels of risperidone and its metabolite. Some authors have suggested that this effect may contribute to the sometimes milder long-time course of schizophrenia in women, usually with better outcome, less hospital care, and a better clinical response to treatment with antipsychotic drugs (27–29). Also in studies on the acute antipsychotic effect of neuroleptic treatment it has been shown that there are more responders among women than among men (30) and that men require higher optimal doses (31). All this might suggest that prolactin can have antipsychotic effects, in line with the hypothesis presented by Zhang et al. (26) (v.s.). Our findings do not support this assumption. There was no significant correlation between prolactin levels on one hand and any of the PANSS items, the PANSS total score (positive, negative, and general) and the four PANSS factors. This indicates that prolactin does not have any symptom-reducing effect. However, one unexplained finding of the present study was that women remained on risperidone treatment over the 5-year period to a much larger extent than men, which might mean ‘better treatment response’ and women on risperidone had much higher prolactin levels than those treated with other compounds. This is discussed in more detail in a separate report (32).

Earlier studies have shown that different factors like age, sex, duration of illness and class of antipsychotic drug contribute to the strength of the prolactin response during antipsychotic treatment (33–37). We could identify only two factors that contributed: sex and treatment with risperidone. This was not an expected finding as at least the conventional antipsychotics (38) and also some of the atypical ones have antidopaminergic properties that should induce an increase in prolactin level similar to that obtained by risperidone. In the present study only risperidone influenced prolactin levels significantly. Other antipsychotics, including older and typical ones were in the same range as for drug-free patients. This finding differs from data on a conventional type antipsychotic compound published by Johnstone et al. (39). They found that both dosage and levels of flupenthixol were significantly related to prolactin levels. It is possible that antipsychotics with different receptor profiles induce different prolactin responses and that risperidone with affinity for both dopamine D2 and serotonin 5-HT2 receptors influence the tubero-infundibular system in a different way than for example flupenthixol with less 5-HT2 receptor affinity. However, most previous studies have not had such a long follow-up period as 5 years.

One interesting finding of the present study was that the risperidone metabolite rather than the mother substance is implicated as the prolactin-increasing agent, in spite of their substantial similarities in terms of receptor affinities and antipsychotic effects. One simple explanation might be linked with the half-life in plasma of mother substance and metabolite, in interaction with diurnal variations in prolactin secretion. However, there are other more theoretically interesting possibilities (v.s.).

A reduction of prolactin response with time has been found in earlier studies (40, 41). This could indicate an induction or supersensitivity in both pituitary and striatal dopaminergic systems with increasing age and duration of illness. Rao and Brown (36) found that already during the first year of treatment with haloperidol or thioridazine the serum concentration of prolactin decreased in the group treated with haloperidol but did not decrease in the group treated with thioridazine. They assumed that during treatment with some antipsychotic drugs, a functional tolerance might develop in the tubero-infundibular dopamine system. However, their findings can also be explained with reference to the low lipophilicity of thioridazine and the penetration of the blood–brain barrier of the tubero-infundibular dopamine receptors. This explanation cannot be valid for risperidone and its metabolite, which are both
lipophilic. Further studies are needed to clarify this, also motivated by the fact that 9-OH-risperidone will be marketed as a new atypical antipsychotic drug.

Sexual dysfunction is reported to be frequent in patients with schizophrenia, especially in men. Clinical reports indicate that atypical antipsychotics are associated with a lower incidence of sexual adverse effects than most of the older compounds. In the present study sexual side effects were common, both in men and women. The prevalence of reduced sexual desire was reported in half, and orgasmic dysfunction in one-third of the total sample. About one-fourth of all men reported erectile dysfunction and/or ejaculatory dysfunction. The most common sexual side effect reported in women was amenorrhea. There was no correlation between sexual side effects and increase in prolactin levels, neither in men, nor in women. Sexual function is complex and could be affected both by schizophrenia itself and by the antipsychotic drugs, which target many receptor systems. Our data do not support the assumption that sexual dysfunction among psychotic patients treated by antipsychotic drugs is caused to a substantial degree by prolactin increase, as suggested by Cutler (42).

In a study by Baptista et al. (43) it was shown that prolactin correlated positively with BMI in a group of out-patient men treated with antipsychotics. In male in-patients there was a correlation between prolactin and waist–hip ratio. This is contradictory to the present findings: if anything a negative correlation between prolactin levels and BMI in women. The difference between the studies may be that we included both sexes, not only males. Previous data have shown that prolactin stimulates insulin secretion and proliferation of pancreatic cells in pancreatic islets of murine and human origin (44–47). A possible weight-gain effect of prolactin in schizophrenic patients could therefore be attributed to prolactin-induced stimulation of β cells. However, this effect was not corroborated in the present study.

Many of our findings are not fully consistent with previous studies; therefore, it is important to consider factors that may underline these differences. It is a naturalistic multi-center study in which clinicians were free to select treatment once the inclusion criteria were satisfied. The inclusion criteria were wide which can be assumed to produce a substantial heterogeneity among the study patients, but at the same time increases the possibilities to generalise to clinical populations. Risperidone was at that time a new compound associated with hope for more efficient treatment with fewer side effects. This has probably biased patient selection somewhat towards patients who did not respond well to previous treatment options. The drop-out rate immediately after inclusion was large, mainly because some investigators decided to leave the study. Still, drop-out patients differed somewhat from stay-on patients, being slightly more symptomatic. From the first follow-up session, approximately half the patients remained on risperidone over the full study, i.e. enough patients were treated in a uniform manner to uphold statistical power. The other half of the patients were treated in many different ways pharmacologically – each subgroup did not contain enough patients to provide sufficient statistical power for detecting small or moderate differences in outcome variables. Therefore, conclusions with respect to risperidone are robust, i.e. that 9-OH-risperidone appears to be particularly involved in raising the prolactin level, that this increase is more pronounced in women, that adaptation to this effect takes place over the full time range of 5 years, and that we could not identify any association between a high prolactin level on one hand, and symptoms or significant side effects. If so, maybe there is no cause to be very worried over the increase in prolactin level induced by some antipsychotic compounds. It is reasonable to assume that the same findings would be reproduced in patients on long-acting risperidone.

Acknowledgements

A number of Swedish psychiatrists at 11 sites were involved in collecting data, to whom we would like to express our sincere gratitude. Janssen-Cilag, Sweden sponsored the study by a non-conditioned grant, and blood sample analyses were performed in a laboratory in Gothenburg.

Declaration of interest

Jonas Eberhard has held lectures for and received honoraria from Jansen-Cilag, Eli Lilly, and Pfizer, and in addition to his affiliation to the Department of Psychiatry at Lund University, he is currently, since the end of 2001, employed as a medical advisor for H. Lundbeck A/S, Copenhagen. Eva Lindström has held lectures for and received honoraria from Jansen-Cilag, Pfizer, and Bristol-Myers Squibb. Maria Holstad: none. Sten Levander has been a speaker and received honoraria from Jansen-Cilag, Lundbeck, and Organon. The authors conducted the data analyses. The protocol can be obtained from Eva Lindström (eva.lindstrom@akademiska.se).

References

1. HÖKFELT T, LUNGDAL A, FUXE K, JOHANSSON O. Dopamine nerve terminals in the rat limbic cortex: aspects of the
Prolactin during 5 years of risperidone treatment


42. **Cutler AJ.** Sexual dysfunction and antipsychotic treatment. Psychoneuroendocrinology 2003;28(suppl. 1): 69–82.