

# Prolactin Levels During Long-term Risperidone Treatment in Children and Adolescents: a Cross-sectional Study

Kurt Buhagiar and Joseph R. Cassar

Department of Psychiatry, Mount Carmel Hospital, Attard, Malta

Corresponding author: Kurt Buhagiar, Department of Psychiatry, St. Ita's Hospital, Portrane, co. Dublin, Republic of Ireland; Email: [kurt.buhagiar@ucdconnect.ie](mailto:kurt.buhagiar@ucdconnect.ie)

## Abstract

**Objective:** Risperidone is a commonly prescribed antipsychotic in children and adolescents with a wide spectrum of mental illnesses. Of all atypical antipsychotics, it has the greatest propensity to induce hyperprolactinaemia. This study assessed the correlation between treatment with risperidone and serum prolactin levels in an out-patient paediatric population.

**Methods:** A cross-sectional retrospective medical chart review of 25 children (18 males and 7 females, age range 7–15 years, mean age  $11.2 \pm 2.0$  years) treated solely with risperidone (mean dose  $1.6 \pm 0.9$  mg per day) was undertaken. Serum prolactin levels were obtained after at least 3 months (mean  $30.4 \pm 12.7$  months) of treatment.

**Results:** Eighty percent of subjects were found to have serum prolactin above the upper limit of normal, with no statistically significant gender difference in the extent of prolactin elevation. Risperidone-induced hyperprolactinaemia was found to be dose-dependent (males,  $r = 0.55$ ,  $p = 0.017$ ; females,  $r = 0.92$ ,  $p = 0.003$ ). No correlation is present between the duration of treatment and serum prolactin levels.

**Conclusions:** Risperidone-induced hyperprolactinaemia in children is a real adverse effect with potentially serious clinical implications. However, neither this study nor previously published studies have formally evaluated these adverse effects as yet. Further studies are thus required in this special age group to address this issue (*German J Psychiatry* 2008; 11: 45-50).

**Keywords:** Antipsychotic drugs, hyperprolactinaemia, prolactin, risperidone, children, adolescents

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## Introduction

Of all commercially available atypical antipsychotic drugs, risperidone is believed to be the most prolactin-elevating agent (Kleinberg et al., 1999; Alfaro et al., 2002; Turrone et al. 2002; Saito et al. 2004) through blockade of dopamine type 2 (D<sub>2</sub>) receptors on lactotrope cells in the anterior pituitary gland (Halbreich & Kahn, 2003). In children, risperidone-induced hyperprolactinaemia is thought to be even more pronounced than in adults (Saito et al., 2004).

Risperidone has been reported to be safe and efficacious in paediatric populations with disruptive behaviour disorders (DBD), pervasive developmental disorders (PDD) and mental retardation (MR), both from short-term studies (McDougle et al., 1998; Nicolson et al., 1998; Snyder et al., 2002; Aman et al., 2005; Croonbergs et al., 2005) and from long-term studies (Zarcone et al., 2001; Turgay et al., 2002; Findling et al., 2004). Its use in paediatric bipolar disorder has been supported by the positive outcome of a short-open-label trial in 30 youths (Biederman et al., 2005). Risperidone has also found its place in the treatment of children with tic disorders (Bruun & Budman, 1996; Dion et al., 2002), psychotic disorders (Armenteros et al., 1997) and obsessive-compulsive disorders (Fitzgerald et al., 1999).

However, since risperidone treatment in children with these conditions tends to be prolonged (Hellings et al., 2005), the adverse effects of long-term antipsychotic-associated hyperprolactinaemia should not be overlooked (Cesena et al., 2002).

Very few studies have actually reported the adverse effects of prolonged prolactin elevation in children, which include stunted growth, delayed sexual development and impaired functioning (Colao et al., 1998), galactorrhoea (Hardan et al., 1996), gynaecomastia, weight gain and osteoporosis (Pappagallo & Silva, 2004). Moreover, a number of as yet unestablished adverse effects may be attributed to the ubiquitous distribution of various prolactin-binding sites in the body (Wieck & Haddad, 2003). Thus, in general little substantive data is available about the possible adverse effects of sustained risperidone-associated hyperprolactinaemia in this age group due to lack of long-term studies (Masi et al., 2001). Therefore, given the paucity of data on the effects of prolonged risperidone-induced hyperprolactinaemia in children, some authors have suggested switching to a prolactin-sparing antipsychotic like quetiapine (Toren et al., 2004) or treatment with cabergoline (Cohen & Biederman, 2001).

This study was designed in an attempt to add to the sparse findings on the effect of risperidone monotherapy in children with mental illnesses with respect to its prolactin-elevating effect. It therefore addressed the following questions pertinent to such prolactin elevation: (a) To what extent does risperidone raise the level of prolactin in youngsters? (b) Is the degree of prolactin elevation related to gender? (c) Is the elevation of prolactin related to the dose of risperidone and to the duration of maintenance treatment?

## Methods

### Subjects

The patient population studied consisted of children 7 to 15 years of age inclusive (mean age  $11.2 \pm 2.0$  years). These children, all of whom are Caucasians, attend Child Guidance Out-patient Clinic, St Luke's Hospital, Malta and suffer from mental health disorders with significant emotional and behavioural disturbance, including DBD, PDD, MR, and childhood-onset psychotic disorders.

Youngsters were chosen to be included in the analysis if they were less than 16 years of age, and maintained on risperidone for at least 3 months. Concomitant treatment with a second antipsychotic drug (both typical and atypical) or any other drug that is known or might possibly interfere with dopaminergic pathways (including antidepressants and stimulant drugs) excluded the youngsters from analysis. Use of mood stabilisers, any other anticonvulsant drugs or any medication deemed to be necessary was not considered to be a confounding factor.

Thirty-eight (38) children satisfied these criteria, their guardians were contacted by telephone and asked to give informed consent. Twenty five subjects ( $N = 25$ ) were granted consent

to participate in the prolactin-measurement study, 18 males (age range: 7-15; mean age  $11.1 \pm 2.2$  years) and 7 females (age range 9-13; mean age  $11.6 \pm 1.4$  years). Subjects were therefore stratified into two subgroups according to gender.

An attempt to study a parallel comparative group of youngsters at our out-patient clinic who were treated with olanzapine was unsuccessful, as all subjects were simultaneously treated with a second psychotropic agent. Hence, they did not fit in the previously defined inclusive criteria.

Ethical approval was obtained from the Quality Assurance/Improvement Initiative, Health Division, Government of Malta.

### Study Design and Procedures

The study took the form of a retrospective, cross-sectional chart review of youth exclusively maintained on risperidone. Blood samples to assay serum prolactin levels were drawn over three weeks in December 2006. The defined standard protocol was to draw these blood samples by venipuncture early in the morning following administration of their morning dose of risperidone by the guardians and collect them in EDTA vacutainers (Becton Dickinson Vacutainer Systems, UK). In most instances, baseline levels of prolactin prior to starting risperidone were unavailable for comparative purposes.

Blood samples were eventually sent for assaying at St. Luke's Hospital Clinical Chemistry Laboratory, where an immunoassay was used for quantification. The normal reference range of prolactin at this laboratory was 53-360 mU/l for males and 40-530 mU/l for females.

Generally no baseline weight of the youngsters was available in the charts, as the initial dose of risperidone was usually started empirically by our predecessors in the clinic, likely based on severity of symptoms and the predicted response to treatment. This therefore prevented calculating pharmacokinetic correlations in terms of weight-adjusted dosages. Furthermore, given the weight-increasing effects of risperidone (Turgay et al., 2002), taking current weight into account without having a baseline to compare to, would have added a further obstacle.

## Results

Out of 25 subjects studied, 80% (15 males, 5 females) were found to have serum prolactin above the upper limit of the normal reference range. In males, mean prolactin was  $572.7 \pm 233.2$  mU/l, whereas in females mean prolactin was  $577.6 \pm 268.3$  mU/l. The mean increase of prolactin above the upper limit of normal in males was thus  $1.6 \pm 0.6$  times, compared to  $1.4 \pm 0.5$  in females. This seeming gender difference in the extent of prolactin elevation was of no statistical significance ( $t = 1.94$  at 0.05 level of significance). No data was generally available to compare elevation of prolactin with baseline values.

**Table 1. Characteristics of children treated with risperidone and their serum prolactin levels**

Subject number	Age	Dose mg/day	Months on drug	Prolactin level (mU/l)
<b>Males</b>				
1	7	2	23	281
2	8	3	36	688
3	9	1.5	42	610
4	9	1.5	42	456
5	9	2	35	847
6	10	1	16	566
7	11	0.5	20	402
8	11	1	26	552
9	11	1	29	260
10	11	0.75	29	562
11	11	1	45	458
12	12	4	34	838
13	12	1	51	711
14	12	3	26	1141
15	13	1	13	196
16	14	1	14	744
17	15	2	42	484
18	15	2	28	512
<b>Mean</b>	<b>11.1</b>	<b>1.6</b>	<b>30.6</b>	<b>572.7</b>
<b>SD</b>	<b>2.2</b>	<b>0.9</b>	<b>11.1</b>	<b>233.2</b>
<b>Females</b>				
1	9	2	44	912
2	10	1.5	6	645
3	12	1.5	12	682
4	12	0.5	53	93
5	12	1.5	38	650
6	12	2	34	624
7	13	1	21	324
<b>Mean</b>	<b>11.6</b>	<b>1.6</b>	<b>29.6</b>	<b>577.6</b>
<b>SD</b>	<b>1.4</b>	<b>0.5</b>	<b>17.3</b>	<b>268.3</b>

The mean duration of treatment with risperidone was 30.4 ±12.7 months. The mean daily dose of risperidone was 1.6 ±0.9 mg per day. Table 1 summarises this data.

*Dose of risperidone and prolactin.* In order to establish whether a correlation exists between the dose of risperidone and serum prolactin levels, a Pearson’s product moment correlation was conducted for each set of variables according to gender (Figures 1 and 2). A statistically significant correlation between dose of risperidone and prolactin elevation could be demonstrated in both male ( $r = 0.55, p = 0.017$ ) and female ( $r = 0.92, p = 0.003$ ) subgroups.

*Duration of risperidone treatment and prolactin.* To assess the possible correlation between length of maintenance treatment with risperidone and level of serum prolactin in children, a Pearson’s product moment correlation was carried out. No statistically significant association was present in both males ( $p = 0.46$ ) and females ( $p = 0.59$ ).

*Type of formulation and prolactin.* For the larger male subgroup, an independent samples *t*-test was performed to assess any

causal relationship between serum prolactin and the type of formulation, that is, generic or proprietary. No statistically significant difference in the level of hyperprolactinaemia induced by either type of formulation could be demonstrated ( $t = 0.78$  at 0.05 level of significance).

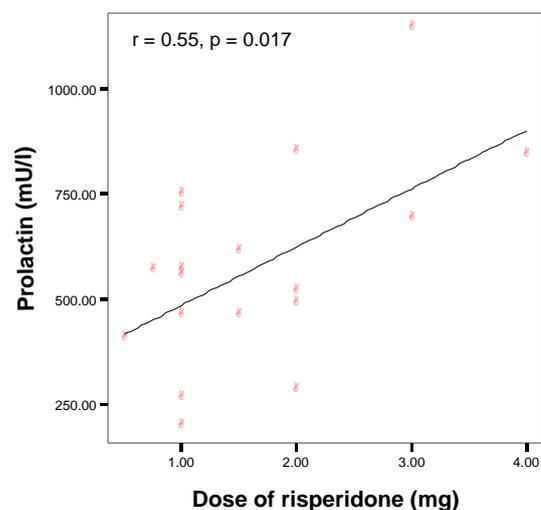
## Discussion

Our retrospective, cross-sectional study assessing an out-patient population of 25 children with mental illnesses is greatly indicative that risperidone is linked to significant elevation of serum prolactin during prolonged periods of treatment between 6 and 53 months.

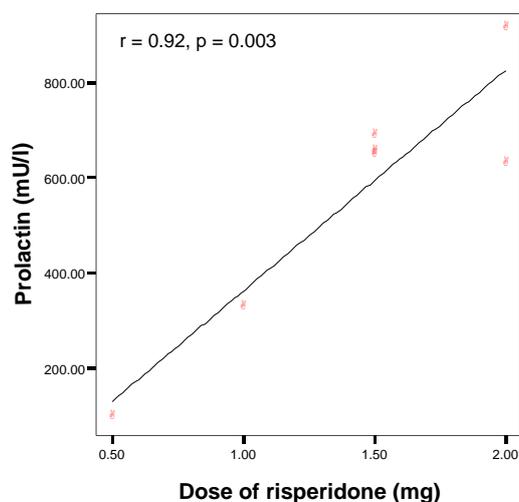
Of 25 youngsters treated with risperidone, 20 (80%) were found to have prolactin above the upper limit of the reference range. This outcome compares well with previous literature describing the incidence of risperidone-induced hyperprolactinaemia in a paediatric population: 76% (Masi et al., 2001), 71% (Saito et al., 2004) and 68% (Stevens et al., 2005). Similar frequencies of risperidone-induced hyperprolactinaemia have been estimated in adults (Kinon et al., 2003). In the latter open-label study, the point prevalence of hyperprolactinaemia in females taking risperidone in long term was 88%.

On the other hand, this data contrasts sharply with findings published by Aman et al. (2002). In this double-blind, placebo controlled study to assess the efficacy and safety of risperidone in children with disruptive behaviour disorders, prolactin levels at six-week endpoint were only statistically high in boys. In girls, the mean increase in prolactin after acute treatment was of no different than placebo. Even more notable are the findings presented by Turgay et al. (2002) from their 48-week open-label study to investigate the efficacy and long-term effects of risperidone in children with

**Figure 1. Prolactin levels of 18 boys maintained on risperidone (mean dose 1.6 ±0.9 mg per day)**



**Figure. 2. Prolactin levels of 7 girls maintained on risperidone (mean dose  $1.6 \pm 0.5$  mg per day)**



DBDs and subaverage IQs. Although hyperprolactinaemia was initially observed in both female and male subjects, reaching its peak within 4 weeks of treatment with risperidone, the level of prolactin declined thereafter to within the normal range. At the end of the study, the mean prolactin levels were greater than the baseline only in boys, yet remaining within the normal range. Findling et al. (2003) pooled data from 5 clinical trials assessing long-term risperidone in children with DBDs and subaverage intelligence and likewise revealed that while serum prolactin level rises within the first 2 months of treatment with low-dose risperidone, it consistently steadily declined thereafter. Ultimately, this hyperprolactinaemia nearly resolved and in some instances even resolved completely after 3 to 5 months.

In complete contrast to this, none of our subjects had been on acute treatment with risperidone at the time of sampling, and yet 80% of subjects were shown to have elevated prolactin levels. This means, that contrary to the findings of Turgay et al. (2002) and Findling et al. (2003), hyperprolactinaemia tends to persist during maintenance therapy even after 4 years (male subject 13). Indeed, even in adults, antipsychotic-induced hyperprolactinaemia tends to be marked and sustained following maintenance treatment both with conventional agents (Zelaschi et al., 1996) and with risperidone (Wieck & Haddad, 2003).

Moreover, our findings suggest that no statistically significant gender difference in the extent of risperidone-induced elevation of prolactin above the upper limit of normal exists in children. To our knowledge, previous studies in children did not take into account sex difference, either because the study was conducted solely on male subjects (Stevens et al., 2005) or the number of female subjects in the study was too small (Masi et al., 2001; Saito et al., 2004). However, this is not the case in adult subjects. In a prospective study of adult subjects with mental retardation and pervasive developmental disorders, Hellings et al. (2005) demonstrated that both acute and maintenance treatment with risperidone in adult

females resulted in significantly greater hyperprolactinaemia than adult males. It is suggested that this tendency for prolactin levels in females to be greater than in males comes by nature of the intrinsic difference in physiology of prolactin (Halbreich & Kahn, 2003). Namely, this is related to the role of oestrogen in the regulation of oestrogen secretion. Likewise, this view could be extrapolated to explain the absence of gender difference in the effect of risperidone in pre-pubertal children.

Our findings suggest that risperidone-induced prolactin elevation is dose-dependent. Kleinberg et al. (1999) pooled data from 2 large random, double-blind controlled clinical trials investigating risperidone, haloperidol and placebo in large samples of adult schizophrenic patients. A significant association between dosage of risperidone and hyperprolactinaemia was unequivocally demonstrated. Similarly, Turrone et al. (2002) followed a small population of schizophrenic adults on maintenance risperidone, and showed a dose-dependent correlation. However, in paediatric studies, this relationship seems to be somewhat unclear: Masi et al. (2001) found no clear-cut association between risperidone dosage and prolactin elevation. Our data is consistent with the recently published findings by Stevens et al. (2005) suggesting a clear dose-dependent elevation in serum prolactin by risperidone treatment in children.

Given the fact that our clinic is unique in catering for children and adolescents with mental illnesses in Malta, our patients have been regularly followed up for a number of years. Therefore, this allowed a long retrospective time interval of risperidone treatment, providing us with the possibility of assessing duration of treatment and prolactin level. Nevertheless, as reported by Stevens et al. (2005), no statistically significant correlation between duration of treatment and prolactin level could be demonstrated.

What is also striking is that even at small risperidone doses prescribed in children, compared to the recommended dose of 4-8 mg per day in adults (Green, 2000), prolactin elevation is remarkably high. Our mean daily dose of risperidone  $1.6 \pm 0.8$  mg compares well with doses used elsewhere by other authors and deemed to be safe and effective in a population with similar childhood mental disorders: Aman et al. (2002) – 0.02-0.06 mg/kg/day; Malone et al. (2002) – 1.2 mg/day; Snyder et al. (2002) – 0.02-0.06 mg/kg/day; Findling et al. (2004) – 1.5 mg/day.

## Limitations

Our study is limited by the fact that previous knowledge of prolactin levels were not known for comparison, no prospective longitudinal data is available to further assess any changes in serum prolactin levels, the dose of risperidone prescribed was not adjusted to weight of subjects, the number of subjects studied was only 25, and no comparable group on another atypical antipsychotic agent was available. In females, no difference was made with respect to their pubertal states. Moreover, clinical significance of risperidone-induced hyperprolactinaemia was not assessed, although *prima facie*, none of our subjects demonstrated clinically significant effect by nature of their hyperprolactinaemia.

## Conclusion

Long-term risperidone treatment in an out-patient paediatric population with mental illnesses caused a dose-dependent elevation in serum prolactin equally in both males and females, by nature of an inherent property of this antipsychotic agent itself. No association was found between duration of treatment and the degree of hyperprolactinaemia. Given that little conclusive data is available assessing specific clinical consequences of antipsychotic-induced hyperprolactinaemia in children, further studies are required to address this issue. This would eventually resolve the dilemma as to whether switching to a prolactin-sparing antipsychotic in a previously well controlled youngster on risperidone, or possibly even treating the secondary hyperprolactinaemia is warranted.

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