Brief Report

Growth and Sexual Maturation During Long-Term Treatment With Risperidone

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Objective: This study assessed the impact of risperidone on growth and sexual maturation.

Method: The pooled database of five studies included 700 children ages 5–15 years with disruptive behavior disorders. All evaluable patients had received risperidone for 11 or 12 months. Those evaluable for growth also had baseline and 11- or 12-month height measurements (N=350); girls ≥9 years and boys ≥10 years who were evaluable for sexual maturation also had baseline and 11- or 12-month Tanner staging (N=222).

Results: Risperidone-treated children had a mean increase in height 1.2 cm greater than the reference population, and they experienced no delay in progression through Tanner staging. Transient increases in prolactin did not correlate with growth or sexual maturation.

Conclusions: In this retrospective analysis, there was no evidence of statistically or clinically significant growth failure or delay in pubertal onset or progression in children treated for up to 1 year with risperidone.

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Risperidone is a novel atypical antipsychotic that has been proven effective in the treatment of several disorders, including the management of symptoms associated with disruptive behavior disorders in children and adolescents. Five clinical studies of risperidone use of up to 12 months in duration have been conducted in this population (1–5). In these studies, mean prolactin levels peaked within 4 to 7 weeks then decreased toward normal levels by the end of the study (1–5). The long-term data in these trials provide a unique opportunity to investigate the impact of risperidone treatment on growth and sexual development in relation to this transient increase in prolactin.

Method

Data from five multicenter studies were merged: two 6-week, placebo-controlled, double-blind trials (1, 2); two open-label, 48-week extensions of those trials (3, 4); and a 48-week, open-label trial (5). The pooled database included 700 children ages 5 to 15 years with IQs ranging from 35 to 84 and a diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified, according to DSM-IV criteria. The subjects provided verbal and, if capable, written informed consent; signed consent was obtained from the subjects' legal representatives. The dose of risperidone ranged from 0.02 to 0.06 mg/kg/day. Height and Tanner staging data were obtained at baseline (predose) and after 11 or 12 months of risperidone treatment, depending on the trials in which the participants were enrolled. Serum prolactin levels were measured before the first dose of risperidone was administered and at similar—but not identical—time points: at 1, 3, 6, 9, and 11 or 12 months postdose. The samples were analyzed at a central laboratory.

The growth population was defined as those who had received treatment with risperidone for 11 or 12 months and had both baseline and 11- or 12-month height measurements recorded. Growth data were compared with two population standards derived from the National Health and Nutrition Examination Survey (6) and growth velocity charts (7). Correlation analyses were conducted between deviations from expected growth and area under the prolactin curve during five time intervals: 0 (predose) to month 1, 0 to month 3, 0 to month 6, 0 to month 9, and 0 to month 11 or 12. In addition, 95% confidence intervals (CIs) were calculated for the mean estimates of deviation from expected growth and correlation coefficients.

The sexual maturation population was defined as girls ≥9 years and boys ≥10 years who had received treatment with risperidone for 11 or 12 months. Evaluable patients had both baseline and 12-month assessments of Tanner staging recorded, in which stages 1 through 5 are used to describe the configuration of pubic hair and genitalia (8, 9). Progression through Tanner staging was compared to the reference populations described by Marshall and Tanner (8, 9). Correlations were conducted between deviations from expected progression and area under the prolactin curve during the same intervals just outlined; 95% CIs were calculated for the mean estimates of deviation from expected maturation and correlation coefficients.

Results

The growth population included 350 children (mean age=10.2 years, SD=2.4; 84% boys, 87.1% Caucasian). The mean dose of risperidone was 1.31 mg/day (SD=0.70). After 12 months, the risperidone-treated children had a mean increase in height of 1.2 cm greater than the reference population (95% CI=0.9 to 1.5) (Table 1), according to population standards derived from the National Health and Nutrition Examination Survey (6). A slightly larger mean increase (1.5 cm) was found when the growth velocity chart (7) was used. There was no statistically significant correlation between the deviation from expected growth and the area under the prolactin curve at any of the five time intervals assessed. Correlation coefficients ranged from a low of 0.035 at month 9 (R^2=0.0013) to a high of 0.099 at weeks 8 to 12 (R^2=0.0097). By the end of the study (month 12), the correlation coefficient was 0.064 (95% CI=

TABLE 1. Observed Versus Expected Outcomes for Height, Growth, Tanner Stage, and Maturation for 700 Children With Disruptive Behavior Disorders Over 12 Months of Risperidone Treatment

	Baseline						12-Month					
	Observed		Expected[a]		Difference		Observed		Expected[a]		Difference	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Height (cm)[b]												
Absolute	139.4	15.5	139.9	13.6	–0.5	8.1	146.3	15.4	145.6	13.6	0.7	8.4
Change							6.9	2.9	5.7	1.2	1.2	2.8
Tanner stage[c]												
Absolute	1.87	1.12	2.16	1.08	–0.29	0.86	2.62	1.27	2.79	1.21	–0.17	0.91
Change							0.74	0.79	0.63	0.32	0.12	0.77

[a] Expected heights were calculated from National Health and Nutrition Examination Survey growth charts posted on the Centers for Disease Control web site (6); expected Tanner stages were calculated as the average of the scale for boys and the average of the scale for girls (8, 9).
[b] 350 children, mean age=10.2 years.
[c] 222 children, mean age=11.9 years.

–0.055 to 0.182), with an R^2 value of 0.0041. That is, only 0.41% of the variation in the deviation from expected growth could be explained by the differences in the area under the prolactin curves.

The sexual maturation population included 222 children (mean age=11.9 years, SD=1.4; 80% boys, 88.3% Caucasian). The mean dose of risperidone was 1.50 mg/day (SD=0.71). At baseline, the risperidone-treated children were a mean of 0.29 Tanner stages behind the reference population (Table 1); after 12 months, they were only a mean of 0.17 stages behind. That is, the risperidone-treated children matured slightly more rapidly than the reference population by a mean of 0.12 Tanner stages, measured on a scale of 1–5 (95% CI=0.02 to 0.22). There was no statistically significant correlation between the deviation from expected sexual maturation and the area under the prolactin curve at any of the time intervals assessed. Correlation coefficients ranged from –0.011 at month 6 (R^2=0.0001) to –0.131 at month 12 (R^2=0.0171). That is, at the end of the study, only 1.71% of the variation in the deviation from expected maturation could be explained by the differences in the area under the prolactin curves.

Discussion

In these analyses, long-term treatment with risperidone (up to 12 months) did not interfere with either growth or sexual maturation. The dose used in these studies was relatively low and within a narrow range; there was no dose-response effect of risperidone on growth and puberty. Despite transient increases in prolactin, the children grew according to published population reference standards and continued to mature as expected when compared with published norms. A limitation of this analysis is the possible differences in demographic characteristics between the pooled database and the comparison populations; however, the data are reassuring in that no interference with either growth or pubertal progression could be demonstrated.

Elevated serum prolactin levels are associated with the use of both conventional and newer atypical antipsychotic medications. Hyperprolactinemia may cause gynecomastia and galactorrhea and may be indirectly associated with menstrual disorders and sexual dysfunction through the effects on estrogen and testosterone. Marked hyperprolactinemia, through indirect effects on hypogonadism, may be associated with osteoporosis. There are few data addressing the effects of modestly elevated prolactin levels associated with the use of antipsychotics. There was no correlation between prolactin levels and growth or sexual maturation.

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