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Review Article

Hyperprolactinemia with Antipsychotic Drugs in Children and Adolescents

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There is increasing use of antipsychotic drugs in pediatric and psychiatry practice for a wide range of behavioral and affective disorders. These drugs have prominent side effects of interest to pediatric endocrinologists, including weight gain and associated metabolic risk factors and hyperprolactinemia. The drugs block dopamine action, thus disinhibiting prolactin secretion. Hyperprolactinemia is especially prominent with first-generation antipsychotics such as haloperidol and the second-generation drugs, most commonly risperidone, with some patients developing gynecomastia or galactorrhea or, as a result of prolactin inhibition of gonadotropin releasing hormone from the hypothalamus, amenorrhea. With concern about the long-term effects of antipsychotics on bone mass and pituitary tumor formation, it is prudent to monitor serum prolactin levels in antipsychotic drug-treated pediatric patients and consider treatment with an agent less likely to induce hyperprolactinemia.

1. Introduction

The practice of psychiatry and the shift to noninstitutional care of severe psychiatric disorders are the result of antipsychotic medications, beginning with chlorpromazine in the early 1950s. Approximately 10 other drugs, known as first-generation or typical antipsychotics, followed over the subsequent 30 years. These drugs were effective in treating positive symptoms of psychosis such as hallucination and delusion but did not alleviate the negative symptoms of withdrawal, apathy, cognitive impairment, or loss of affect. Furthermore, they were associated with frequent extrapyramidal symptoms, including acute dystonia, akinesia, akathisia, tardive dyskinesia, and parkinsonism. A series of newer drugs began emerging in 1989, referred to as second generation or atypical antipsychotics, thought to be more effective than the older agents in alleviating the negative, cognitive, and affective symptoms, with fewer extrapyramidal adverse effects [1].

The antipsychotic drugs differ in their side effect profiles, as they affect different neuroreceptors (histamine, α-adrenergic, muscarinic, dopamine, or serotonin). The principal concern for endocrinologists with the newer drugs has been the metabolic effects of weight gain, glucose intolerance, hyperlipidemia, and hypertension [2]. This is particularly important with the increasing use of these agents in pediatrics to treat bipolar disorder, schizophrenia, autism, oppositional and other behavior disturbances, Tourette disorder, and pervasive developmental disorder. In 2003-2004, 1% of all pediatric visits resulted in the prescription of atypical antipsychotic medication [3]. The importance and implications of the metabolic side effects of atypical antipsychotics for pediatric patients have been recently reviewed [1, 4].

This paper will examine the side effect of hyperprolactinemia in children and adolescents treated with antipsychotic drugs.

2. Physiology

Prolactin, a 198-amino acid polypeptide, is secreted by the anterior pituitary lactotroph cells in a pulsatile manner with 13-14 peaks per day, the peak amplitude ~60% above nadir [5]. There is also a marked circadian variation with maximum secretion ~4 hours from sleep onset and

minimum ~6 hours after waking [6]. Thus, there can be as much as a fourfold variation in level depending on the time of day or night sampling is done; there are also transient mild increases related to meals, stress, and sexual activity [7]. Prolactin levels are higher during menstrual midcycle and the 2nd half of the cycle. During pregnancy, levels rise 10–20-fold, reaching 200 μg/L at term and 300 μg/L during nursing [8]. Normal upper limit range is 15–25 μg/L [7].

Prolactin stimulates breast enlargement during pregnancy and milk production during lactation, while reducing libido and fertility, which may have evolutionary/survival significance.

Secretion of prolactin is inhibited predominantly by dopamine produced in the tuberoinfundibular neurons of the hypothalamus, released from nerve endings in the median eminence and carried through the portal hypophyseal circulation to the pituitary, there binding to dopamine D_2 receptors on lactotrophs, inhibiting prolactin gene transcription [9]. Antipsychotic drugs are thought to disinhibit prolactin secretion by D_2 receptor blockade. Serotonin stimulates prolactin secretion via serotonin 5-HT_{1A} and 5-HT_2 receptors. Estrogens, binding to specific intracellular receptors in lactotrophs, enhance prolactin gene transcription and synthesis [6]. They also inhibit dopamine synthesis in the tuberoinfundibular neurons and reduce D_2 receptor levels on lactotrophs in animal models [10, 11].

3. Effects of Hyperprolactinemia

Gonadotropin releasing hormone (GnRH), released in a pulsatile manner from the hypothalamus, stimulates release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary. Prolactin inhibits the release of GnRH in the hypothalamus. The positive feedback of estradiol on LH secretion in women is also blocked. Consequently, estrogen levels in women and testosterone levels in men are suppressed, with marked individual variability in the prolactin level causing gonadal hypofunction.

In children and adolescents, hyperprolactinemia resulting from prolactinomas, which are rare, can result in galactorrhea, amenorrhea, gynecomastia, and maturational delay with growth failure [12]. Of concern is the potential effect of the induced hypogonadotropism state on the critical peak bone formation of adolescence and the maintenance of bone density through adulthood.

4. Effects of Psychotropic Drugs on Prolactin Secretion

Psychiatric disorders may be associated with modest elevations in serum prolactin concentrations as a stress phenomenon [13]. Further prolactin elevation can be measured within minutes to hours after the start of treatment with first-generation antipsychotic drugs, with levels up to 10-fold after several weeks at therapeutic dosages. Levels typically fall to normal within 2 to 4 days of stopping the drugs but may take up to 3 weeks to return to normal [14].

In adult psychiatric patients clozapine and quetiapine did not raise plasma prolactin levels at any dosage. Olanzapine only did so at higher dosages, but risperidone and amisulpride caused marked, sustained increase in serum prolactin levels in a substantial number of patients [14]. Aripiprazole, a relatively new atypical antipsychotic, also does not appear to increase prolactin levels [15]. Ziprasidone caused only transient elevations in psychiatric patients and healthy volunteers [16].

A review published in 2004 of 14 reports of the effects of both first- and second-generation antipsychotic agents in children and adolescents included 276 patients of whom 49 had prolactin elevations [17]. A report of 35 patients aged 9–19 years found no prolactin elevation with clozapine, but in 9 of 10 with haloperidol and 7 of 10 with olanzapine [18]. In another study of 11 outpatients aged 4–17 years treated with risperidone, 9 developed hyperprolactinemia of whom one had amenorrhea, and one had gynecomastia [19]. A further study reported that prolactin levels were increased in all 34 patients aged 5–14 years treated with risperidone [20]. Hyperprolactinemia was also noted in pediatric patients using ziprasidone and olanzapine. As with adults, ziprasidone- associated prolactin elevation was mild and transient, but associated with mild gynecomastia [21] and in one case with galactorrhea that resolved after drug discontinuation [22]. Two studies of the effects of quetiapine led to slightly differing results: one showed no increase in prolactin levels in 10 12–15-year-old children while the other study of 15 13–17-year-olds found a slight increase of no clinical significance, from a mean of 11.3 to 14.4 ng/mL [17]. Clozapine was not associated with increased prolactin levels, and the single patient who developed galactorrhea with risperidone had resolution of the problem when switched to clozapine [23].

A retrospective study analyzed prolactin levels and hyperprolactinemia attributable side effects from 5 clinical trials involving 592 children and adolescents of subaverage intelligence with conduct or other disruptive behavior disorders aged 5 to 15 years treated with risperidone. There was a weak effect of risperidone on prolactin concentrations during short-term treatment and lesser effect with long-term treatment, with side effects of gynecomastia, amenorrhea, or galactorrhea in only 2.2% [24]. These relatively benign findings have been attributed to low drug dosage for behavioral rather than psychiatric disorders and decreasing compliance over time [25].

Quite different findings emerged from a small double-blind placebo-controlled study of the effect of relatively low dose risperidone on prolactinemia in 10 children and adolescents with mental retardation and pervasive developmental disorders. Prolactin levels approximately tripled, and this increase was sustained for a mean 33 weeks of treatment [26].

Three adolescents were reported with risperidone-induced hyperprolactinemia resulting in gynecomastia in one boy that cleared and did not recur with olanzapine, gynecomastia with galactorrhea in another boy with comparable prolactinemia that resolved when he was switched to clozapine, and amenorrhea and galactorrhea in the third patient that resolved when she was changed to quetiapine.

Their prolactin levels were 2100, 1670, and 1990 mIU/L (58, 46, and 55 μg/L) when they were hyperprolactinemic and reduced to 63, 90, and 191 mIU/L (2, 2.5, and 5.3 μg/L) after resolution [27]. Among 10 psychotic adolescents treated with risperidone, Holzer and Eap had 3 males developing gynecomastia and 2 females developing galactorrhea, along with 3 others having hyperprolactinemia without symptoms [25].

Sixteen adolescents aged 13–17 years with subaverage intelligence and disruptive behavior disorders treated with olanzapine for 8 weeks had significant elevations in serum prolactin levels, from baseline 9.7 ± 6.1 to 24.8 ± 19.8 (SD) μg/L without any symptoms or signs of hyperprolactinemia [28].

A study from Italy compared short- and long-term effects on prolactin of risperidone and olanzapine in 42 children and adolescents treated for a year [29]. They found that after adjusting for dose and the greater potency of risperidone, the increase in prolactin levels during risperidone treatment was 10.7 times higher than that during olanzapine treatment. Only one subject had a symptom of hyperprolactinemia, transient mild galactorrhea with risperidone which resolved without a change in therapy. Similarly, a randomized comparison of quetiapine and risperidone in 22 15–18-year-old adolescents with new-onset psychosis found prolactin elevation in 91% of those treated with risperidone versus 9% of those treated with quetiapine [30].

Dutch investigators have recently conducted an extensive literature review of studies of antipsychotic medication effects on prolactin level and associated side effects in children and adolescents [31]. They found 29 publications with study durations longer than 3 weeks. Twenty of these were concerning risperidone, 7 olanzapine, 5 quetiapine, 4 haloperidol, 3 pimozide, 2 clozapine, and 1 ziprasidone. They found that all antipsychotics with the exception of clozapine, ziprasidone, and quetiapine increased the mean prolactin level from 8 to 25–28 ng/mL. The incidence of hyperprolactinemia was 90% with haloperidol, 80% with pimozide, 62% with risperidone, 31% with olanzapine, and 12% with quetiapine. Risperidone, olanzapine, and pimozide were seen to induce a persistent elevation in prolactin levels. Associated gynecomastia, galactorrhea, or irregular menses were reported in 4.8% of the children and adolescents. Data from this review and subsequent reports are summarized in Table 1. Interpretation of the numerous studies is confounded by variation in study design, diagnoses, dosages, and age distribution, varying use of concomitant medication, short duration of some studies, compliance uncertainty, lack of prolactin baseline values (one fourth of the studies analyzed by Roke et al. [31]), and other missing data as noted in the table. Furthermore, single measurements of prolactin are subject to diurnal variation and stress influence. There may also be publication bias, as all data on prolactin values from manufacturers' files have not been published [31]. The effects of hyperprolactinemia may be underestimated because they depend on self-report, and may be mistaken for common adolescent problems of gynecomastia and irregular menstrual cycles.

The degree of hyperprolactinemia induced by short-term risperidone treatment in children and youth is dose dependent [17, 33]. This dose dependency is linked to plasma concentrations of both risperidone and its active metabolite 9-hydroxyrisperidone [33]. CYP2D6 is primarily responsible for the conversion of risperidone to 9-hydroxyrisperidone. In an examination of the possible role of activity of this enzyme in risperidone-induced prolactin release in children, Troost et al. [34] found a positive correlation of the fourfold elevation in serum prolactin level at 8 and 24 weeks with dose per kilogram body weight ($r = 0.65$, $P < .001$), number of functional CYP2D6 genes, serum 9-hydroxyrisperidone concentration ($r = 0.66$, $P < .001$) and negative correlation with the risperidone/9-hydroxyrisperidone ratio ($r = -0.57$, $P = .004$) but not with risperidone concentration ($r = -0.24$, $P = .26$). Thus, more rapid CYP2D6 metabolism may be a risk factor for hyperprolactinemia with risperidone. Polymorphic variation in the dopamine D2 receptor may be another pharmacogenetic factor determining risk for risperidone-induced hyperprolactinemia in children and adolescents. Two variants were identified that were associated with higher prolactin concentration in a study of 107 patients treated for up to 3 years [32].

Because second-generation antipsychotics are being increasingly prescribed for children and adolescents with conditions that are not psychoses and that are also treated with stimulants, the potential mitigating effect of the stimulants on the side effects of the antipsychotics has been examined [35]. Stimulant drugs have opposite effects on the dopamine receptor than do the antipsychotics. Subjects were 153 4–19-year-olds treated with antipsychotics, 71 of whom were coprescribed stimulants. The antipsychotic drugs included risperidone (33%), aripiprazole (30%), quetiapine (18%), olanzapine (12%), and ziprasidone (6%). In addition to no effect of cotreatment with stimulants on the side effect of hyperprolactinemia, there was no effect on body composition, metabolic parameters, sedation, or overall efficacy of the antipsychotic agent.

5. Potential Long-Term Effects of Psychotropic Drugs

5.1. Bone Mineral Density (BMD). Antipsychotic-induced hyperprolactinemia in adults with schizophrenia has been associated with reduced BMD and increased fracture risk [36, 37]. The initial report of the effect of psychotropic drugs on BMD in children was a cross-sectional study that involved 83 boys aged 7 to 17 years treated with risperidone for an average of 3 years and selective serotonin reuptake inhibitors (SSRIs) [38]. With adjustment for the stage of sexual maturation, height, and body mass index, a negative association was found between serum prolactin level and trabecular volumetric BMD at the distal radius. Furthermore, treatment with SSRIs was associated with lower trabecular BMD at the radius and BMD Z-score at the lumbar spine. Lumbar spine BMD Z-score did not correlate with prolactinemia. In females with prolactin secreting tumors, hyperprolactinemia effects on BMD are mediated

Table 1: Effects of risperidone, olanzapine, haloperidol, quetiapine, clozapine, ziprasidone, and pimozide on prolactin (PRL) level and PRL related side effects [gynecomastia (GCM), galactorrhea (GLR), and irregular menses (IM) in children and adolescents. Weighted averages (adjusted for numbers of subjects per study) are given for the analysis of Roke et al. [31] with the number of studies analyzed shown in parentheses. Subsequent individual studies are separately indicated, with standard deviations in parentheses. Dashes indicate absent data.

	Drug	Number	Age (years)	Dose (mg/day)	Duration (weeks)	PRL baseline ng/mL	PRL endpoint ng/mL	% with PRL >nl upper limit	% GCM	% GLR	% IM
Roke et al. [31] (20)	risperidone	1390	9.7	1.6	34.8	8.2	21.6	61.7	3.0	0.5	6.2
Migliardi et al. [29]	risperidone	6 (female)	12.8 (2.3)	1.9 (1.1)	52	8.4 (2.1)	23.4 (7.6)	—	—	*	0
		22 (male)	10.1 (2.8)	1.7 (1.2)	52	6.5 (1.9)	14.9 (8.6)	—	0	—	—
Swadi et al. [30]	risperidone	11	<19	—	6	—	—	91	—	—	—
Calarge et al. [32]	risperidone	107	7–17	—	mean-36	—	—	50	8	11	33
Roke et al. [31] (7)	olanzapine	170	14.4	2.7	28	11.1	24.2	31	6.2	2.8	2.4
Migliardi et al. [29]	olanzapine	6 (female)	14.3 (2.1)	6.7 (3)	52	8.8 (3.8)	18 (5.2)	—	—	0	0
		7 (male)	14 (1.9)	7.5 (2.5)	52	7.8 (2.4)	11.3 (4.9)	—	0	—	—
Swadi et al. [30]	olanzapine	11	<19	—	6	—	—	9	—	—	—
Roke et al. [31]											
(5)	quetiapine	72	13.9	378.5	49.6	8.4	9.3	0	0	0	0
(4)	haloperidol	56	12.7	7.2	6.5	7.7	29.1	90	6.7	0	15.4
(3)	pimozide	46	10.3	3.7	21.2	9.3	24.7	80	—	—	—
(2)	clozapine	30	14.5	270	6	9.6	11.6	0	0	0	0
(1)	ziprasidone	6	14.5 (1.8)	98 (40)	8.6 (6.6)	8.6 (6.6)	12 (8)	0	0	0	0

* One individual transiently without dosage change.

by hypogonadism [39]. However, in this study, serum testosterone concentrations, adjusted for maturational stage, were not affected by hyperprolactinemia, suggesting a direct effect of the hyperprolactinemia on bone turnover [38]. Prolactin receptors have been found in osteoblasts, and animal studies indicate that hyperprolactinemia activates the phosphoinositide 3-kinase pathways via the prolactin receptors to suppress alkaline phosphatase activity [40].

The finding that SSRI treatment was associated with reduced BMD could reflect an effect on prolactinemia. However, no independent effect of SSRIs on prolactin concentration was found in an earlier study by these authors [32], and the negative association between SSRIs and BMD was found after adjustment for numerous covariates including prolactinemia. Serotonin has a role in osteoclast differentiation and activity [41]. The study of Calarge et al. [38] is limited by the dependence on a single measurement of serum prolactin which can vary by time of day and stress level, and absence of measures of bone turnover. The authors recognize that it is premature to make any definitive conclusions about the effect of psychotropic medications on bone mineralization [38].

5.2. Pituitary Tumors. Noting higher-than-expected post-marketing reports of pituitary tumors associated with risperidone, Szarfman et al. [42] analyzed patterns of these tumors in the United States Food and Drug Administration Adverse Event (AE) Reporting System database. They sought disproportionate reporting patterns of pituitary tumor reports for antipsychotics with different affinities for blocking D2 receptors (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and haloperidol). The rank order of the strength of the association between the drug and the development of pituitary tumors corresponded to the affinity of these 7 drugs for the D2 receptor. In children 7–18 years of age, there was 1 AE of pituitary tumor associated with olanzapine and 3 with risperidone. The authors note the importance of these findings for children because the symptoms of a pituitary expanding mass may not be as readily evaluated in those with mental illness or serious behavioral problems and that delayed detection can result in hemorrhage or optic nerve compression.

6. Conclusion

Second-generation antipsychotics are being increasingly prescribed for children and adolescents with a wide range of behavioral disturbances in addition to psychoses, resulting in metabolic and hormonal changes of importance to the consulting pediatric endocrinologist. In addition to weight gain and associated comorbidities of insulin resistance, hyperprolactinemia is a common side effect

resulting from the inhibition of dopamine action. First-generation antipsychotics, particularly haloperidol, and the second-generation antipsychotic drugs, most prominently risperidone, appear to be associated with the greatest risk for hyperprolactinemia; some treated individuals developing hyperprolactinemia will have galactorrhea, amenorrhea, or gynecomastia. Hyperprolactinemia may have a deleterious effect on peak bone mass attainment and increase long-term osteopenia risk, even in the absence of overt symptoms or signs of hyperprolactinemia. This adverse effect may be enhanced by the commonly associated treatment with SSRIs. The effect of psychotropic drugs on bone mass accrual needs further study. The suggestion of a greater risk for pituitary tumors related to drug affinity for D2 receptors also requires continued study. Thus, in addition to surveillance for signs and symptoms of hyperprolactinemia in children and adolescents taking antipsychotic medications, monitoring serum prolactin concentrations is warranted. In the presence of hyperprolactinemia, cessation of antipsychotic therapy or changing to a formulation less likely to raise prolactin levels should be considered.

Disclosure

The author is a consultant to a law firm pursuing litigation with manufacturers of second-generation antipsychotic drugs.

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