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Review Article

Prolactin Serum Concentrations During Aripiprazole Treatment in Youth

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Abstract

Objective: This study aimed to: document the extent of the reduction of serum prolactin (PRL) levels induced by aripiprazole (ARI) treatment in children and adolescents, compare this effect by age group, and shed light on this phenomenon.
Methods: PRL serum levels in unmedicated subjects were compared to those in subjects treated with aripiprazole to calculate the rate of subnormal PRL levels during aripiprazole treatment. Next, a literature search was performed to better understand the effects of dopaminergic drugs on PRL levels by age group.
Results: Sixty percent of those treated with aripiprazole exhibited subnormal PRL serum levels versus 8% of unmedicated subjects. The rate of PRL subnormality in response to aripiprazole was half as frequent in adolescents and was minimal in adults. The drug-induced reduction of PRL serum levels became more prominent with increasing doses of aripiprazole and with an increased treatment duration.
Conclusions: With the increasing use of aripiprazole in the United States population, it is important that future research be conducted to explore the potential sequelae of subnormal PRL serum levels in children and adolescents.

Introduction

Aripiprazole (ARI) is an atypical antipsychotic drug that was approved by the United States Food and Drug Administration (FDA) in 2002 for the treatment of schizophrenia in adults. Since then, it has been approved by the FDA for additional indications, including for the treatment of children and adolescents with autistic disorder and bipolar mania as well as for adolescents with schizophrenia. Between September 2009 and March 2011, 369,000 United States youth were prescribed ARI, and during that same period >1,500,000 United States adults were so treated (Taylor 2011).

ARI is a partial dopamine agonist whose major action is at the D2 and 5-HT1A receptor sites. Its dopamine agonist effect likely explains its consistent reduction of serum prolactin (PRL) levels (FDA approved label 2012). Other antipsychotic drugs, for example, risperidone and haloperidol, are primarily D2 antagonists, and these commonly have the opposite effect; they elevate PRL levels (Kinon et al. 2003; Calarge et al. 2009; Melmed et al. 2011). Nonetheless, when risperidone and haloperidol are co-administered with ARI, PRL levels fall to within the normal range (Shim et al. 2007; Kane et al. 2009; Yasui-Furukori et al. 2010).

PRL is primarily secreted by the lactotroph cells of the anterior pituitary gland, but also to a smaller extent by cells in the breast, lacrimal gland, uterus, thymus, and spleen (Tan and Peng 2012). Its release from lactotrophs is mainly under the tonic inhibitory control of dopamine released from tubero-infundibular neurons within the arcuate nucleus of the hypothalamus (Lyon et al. 2009). Like ARI, other dopamine agonists, such as bromocriptine and cabergoline, commonly decrease PRL serum level (Hutchison and Sill 1981; Colao et al. 2008).

In adult females, low PRL is consistently associated with alactogenesis, the failure to lactate after pregnancy. In fact, various drugs that substantially decrease PRL similarly impair lactation (Hutchison and Sill 1981; Colao et al. 2000). Specifically, this has also been the case with ARI, whose use throughout pregnancy has been associated with alactogenesis (Mendhekar et al. 2006a,b; Mervak et al. 2008; Lutz et al. 2010; Gentile et al. 2011; Nguyen et al. 2011; Watanabe et al. 2011). This failure to lactate following pregnancy also characterizes women with an isolated PRL deficiency (Turkington 1972; Spitz et al. 1977; Kauppila 1987; Falk 1992; Douchi et al. 2001), a deficiency that can be the result of a genetic defect (Zargar et al. 1997). Despite its effect on lactation, hypoprolactinemia in women has not been implicated in a decreased likelihood of becoming pregnant, having a normal delivery, or having normal offspring (Widschwendter and Hofer 2012).

In men, hypoprolactinemia has been associated with reduced sperm quality, erectile dysfunction, hypoandrogenism and a relative degree of infertility (Gonzales et al.1989; Ufearo and Orisakwe 1995; Corona et al. 2009). This is thought to be mediated by the

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suppression of testosterone secretion (Suescun et al. 1985; Gonzales et al. 1989). Interestingly, this effect may be reversed, at least partially, by the administration of a dopamine antagonist (Ufearo and Orisakwe 1995).

Very little is known about the prevalence of subnormal levels of PRL in children, adolescents, and adults (Freeman et al. 2000). In order to better understand this hormonal abnormality in the context of treatment with ARI, a search was made to review all reports of PRL serum levels across the age spectrum before and after treatment with ARI, and the pertinent literature on the effects of various PRL concentrations in humans. A primary aim of this work was to quantify available data on subnormal serum levels of PRL induced by ARI across various age groups and present what is known about low PRL levels.

Methods

A thorough search was made in PubMed, PsycInfo®, Embase , Web of Knowledge, and Google covering the period from 1975 to early 2012. The search was intentionally wide in scope. The primary identifying words used were aripiprazole, Abilify,® and prolactin in relation to adverse drug events, side effects, postmarketing surveillance, and influences on the PRL levels of youth (<19 years of age), adolescents (13–18 years of age), children (<13 years of age), women, and men. Other sites searched included the FDA approved label for ARI, FDA reports, FDA related research, laboratory PRL reference norms, reports on the effect of cabergoline and bromocriptine on PRL levels in humans and animals, textbooks in endocrinology, and reference lists within pertinent articles.

The statistical analysis of the PRL serum levels was limited to children <age 13 years because detailed PRL data on ARI-treated adolescents are sparse. Specifically, two large ARI studies in adolescents were not included in the statistical analyses because they had reported no baseline PRL values (Findling et al. 2008a) or only incomplete PRL posttreatment findings (Finding et al. 2009b). Furthermore, other PRL level findings on adolescents after treatment with ARI (Lyon et al. 2009; Erickson et al. 2011) had too few subjects ($n = 23$). Nonetheless, from the two large published trials, the percent of adolescents treated with ARI having subnormal PRL serum levels (<3 ng/mL for females and <2 ng/mL for males) had been reported, and these percentages were used for age group comparisons of PRL serum levels.

Many of the subjects entering clinical trials with ARI had been previously receiving psychotropic medication (Owen et al. 2009). In children and adolescents, the washout of these drugs prior to the baseline laboratory assessments usually ranged from 3 days to 2 weeks; but there were some allowances for continued drug use. For example, three clinical trials of ARI allowed continuing selective serotonin reuptake inhibitor (SSRI) antidepressant drugs (Lyon et al. 2009; Marcus et al. 2011; Stigler et al. 2012). The effect of SSRIs on serum PRL has been inconsistent, with some reporting a slight increase (Foley and Kast 2006), whereas others failed to note this change (Saito et al. 2004; Calarge et al 2009). Other children in trials with ARI were co-prescribed stimulants at baseline and throughout the study (Biederman et al. 2005; Findling et al. 2012; Geller et al. 2012). Stimulants in children have been shown to slightly decrease PRL levels (Lurie and O'Quinn 1991), although other investigators found stimulants did not reduce PRL concentrations (Calarge et al. 2009; Penzner et al. 2009). Consequently, such add-on drugs were not adjusted for in the following analyses.

Numerical data assessments of PRL serum concentration in children (e.g., using means with standard deviations, medians, 95% central ranges, ranges, and baseline findings) were varied and often incomplete. In children entering clinical trials with antipsychotics, nine trials ($n = 690$) reported PRL baseline means and standard deviations (SD). Four baseline population norms with complete data from unmedicated children reported PRL medians and a 95% central range ($n = 105$), and two other laboratories reported PRL norms from unmedicated children with only a 95% central range ($n = 408$). Although most population-based PRL norms in children reported medians (Cook et al. 1992; Soldin et al. 1995; Elmlinger et al. 2002; Aldrimer et al. 2012; Siemens 2012), others used means (e.g., Gassler et al. 2000; Beltran et al. 2008) to convey the central tendency. All the clinical trial data on PRL serum levels were statistically presented as means with SDs.

Because all the clinical trial PRL data were presented as means with SDs, it was decided to base all the statistical analyses on these measures for purposes of age-grouped comparisons. This approach then led to the calculation of the means and SDs from data with medians and 95% central ranges and from data with only 95% central ranges. The pooled SD calculated from the group with means was applied to the group with means calculated from medians and from a 95% central range. To ascertain if the distributions of the weighted means and SDs from the clinical trials were equivalent to the distributions of the weighted means derived from medians, the two groups were compared and their distributions were found not to be significantly different ($p = 0.412$; Mood's Median Test 1988).

Because the weighted means and SDs of the two groups of studies were not significantly different, their findings were combined. The weighted mean and SD of the combined child PRL population ($n = 1203$) then became the total baseline PRL serum level that was used for the analysis of the effect of ARI treatment.

PRL level findings in children <13 years of age are presented as being of both sexes because differences in serum PRL levels by sex in that age group are minimal or absent in all published reference norms (Wiedemann and Jonetz–Mentzel 1993; Soldin et al. 1995; Wudarsky et al. 1999; Elmlinger et al. 2002; Aldrimer et al. 2012). In contrast, with the onset of pubertal development, serum PRL levels start to increase and diverge between males and females with the latter group exhibiting higher concentrations (Elmlinger et al. 2002). The data on boys and girls were, therefore, not statistically distinguished, which also had been the case in the reporting of PRL levels from the ARI clinical trials of children.

The FDA defined subnormal serum levels of PRL in children and adolescents as those <3 ng/mL in females and <2 ng/mL in males (Zhang 2008). This is comparable to the cutoff of the ≤2 ng/mL subnormal PRL level reported by Findling et al. (2008a) and Potkin et al. (2003). Therefore, a statistical analysis was performed to compare the prevalence of subnormal PRL levels (≤2 ng/ml) in normal children as well as in psychiatrically ill children before and after treatment with ARI.

Results

Baseline levels of PRL in children

Table 1 presents prolactin serum level norms in ng/mL by mean age or age group in children aged 7–12 years. These norms consisted of baseline PRL levels from nine clinical trials that included psychiatrically ill children having undergone psychotropic drug washout periods ranging from 3 to 14 days (Aman

Table 1. Prolactin Serum Level (ng/mL) Baselines and Norms by Age and Sex

Reference	*Age (yr)(m)*	n	*Sex*	*Mean PRL level*	*Mean ± SD*
Findling et al. 2011	6.9	96	65% male	5.7	5.7 ± 3.7
Stigler et al. 2009	8.6	25	76% male	9.3	9.3 ± 5.2
Aman et al. 2002	8.7	41	79% male	6.8	6.8 ± 4.2
Marcus et al. 2011	9.5	199	87% male	7.4	7.4 ± 4.8
Zhang 2009	9.7	244	89% male	6.8	—
Geller et al. 2012	10.1	216	50% male	7.2	7.2 ± 4.7
Biederman et al. 2005	10.1	30	73% male	7.9	7.9 ± 5.3
Sallee et al. 2003	10.9	24	79% male	7.2	7.2 ± 2.0
Migliardi et al 2009	11.5	41	71% male	7.3	7.3 ± 2.3
Staller 2006	12.3	18	56% male	6.4	6.4 ± 1.5
Reference norms	*Age range*			*Median*	*95% range*[a]
Siemens 2012	7–8	26	Male	6.7	2.5–25.8
Cook et al. 1992	7–9	203	54% male	—	1.1–12.4
Siemens 2012	7–8	24	Female	7.0	3.1–16.4
Siemens 2012	9–10	31	Male	6.7	4.2–13.4
Siemens 2012	9–10	24	Female	7.3	3.1–16.4
Cook et al. 1992	10–12	217	50% male	—	1.4–11.4

[a]2.5 to 97.5 percentile (central) range.
m, mean; PRL, prolactin.

et al 2002; Sallee et al. 2003; Staller 2006; Stigler et al. 2009; Findling et al. 2011). An FDA review combining mean baseline PRL levels from five clinical trials is included for comparison purposes, but its data were not statistically analyzed with standard deviations or a central 95% range (Zhang 2009). Six PRL reports from major reference laboratories – enrolling healthy children – with medians and/or central 95% ranges were included in the data analysis.

In the nine clinical trials reporting baseline PRL serum levels from psychiatrically ill children ($n = 690$), the mean baseline levels ranged from 5.7 to 9.3 ng/mL with standard deviations ranging from a low of 1.5 to a high of 5.3. The combined *weighted* mean (and SD) PRL serum level was 7.1 ± 4.4 ng/mL. The percent at baseline with a PRL serum level ≤2 ng/mL was 11.8%.

In the six studies of PRL population norms in children ($n = 513$) that included medians and a 95% central range but no SDs, the 95% central PRL levels ranged from extremes of 1.1 to 16.4 ng/mL, with one outlier at 25.8 (Siemens 2012). The weighted PRL mean of this unmedicated population (calculated from the medians and 95% central ranges) was 7.5 ng/mL and the pooled SD was 2.9. The percent with a PRL serum level ≤2 ng/mL was 3.3%.

Impact of ARI on PRL levels in children

Table 2 lists PRL serum levels at baseline and after ARI treatment in clinical trial data of children 6.9–11.6 years of age (e.g., Biederman et al. 2007). The baseline levels are occasionally higher than those in Table 1 because many had been treated with PRL-raising medications (e.g., Owen et al. 2009). After discontinuation of long-term dopamine-blocking antipsychotic drug treatment, it may take several days for PRL levels to return to normal, depending upon the medication's half-life, its route of administration, and its storage in fatty tissues (Haddad and Wieck 2004).

In response to ARI treatment, the median of the mean levels of PRL for children declined from 7 ng/mL to 2 ng/mL (Table 2). Of the six trials including ARI-treated children with available PRL level means and SD at endpoint ($n = 199$), their weighted mean (± SD) PRL level was 1.7 ± 2.1 ng/mL. In this ARI-treated group,

Table 2. Effect of Aripiprazole on Prolactin Serum Level in Children

Reference	*Age (yr.) mean*	n	*% Male*	*Duration weeks*	*Baseline ± SD ng/mL*	*Endpoint ± SD ng/mL*	*Change mean*
Findling et al. 2011	6.9	96	65	12.5	5.7 ± 3.7	1.2 ± 1.1	−4.5
Findling et al. 2012	7.1	30	63	26	—	0.9 ± 0.7	—
Stigler et al. 2009	8.6	25	76	14	9.3 ± 5.2	2.9 ± 3.4	−6.4
Findling et al. 2009b	9.0[a]	12	67	72	7.3 ± 3.7	1.8	−5.5
Marcus et al. 2009	9.5	166	89	8	6.8	1.3	−5.5
Marcus et al. 2011	9.5	148	87	12–52	7.4	1.6	−5.8
Owen et al. 2009	9.7	47	89	8	9.8	3.5	−6.3
Zhang 2009	9.7	134	85	8	6.8	1.4	−5.4
Findling et al 2008b	10	14	61	6	4.5 ± 1.5	2.9 ± 2.6	−1.6
Ercan et al. 2012	10.1	19	95	8	16.6 ± 2.2	2.1 ± 1.5	−14.5
Biederman et al. 2007	11.6	15	58	8	19.4. ± 21.9	3.2 ± 4.7	−16.2

[a]Midpoint in age range of 6–12 years

Table 3. Effect of Aripiprazole on Prolactin Serum Levels in Adults

Reference	*Age (yr) (m)*	n	*% Male*	*Duration weeks*	*Baseline ± SD ng/mL*	*Endpoint ± SD ng/mL*	*Change mean*
Lee et al. 2010	33	21	62	8	15.6 ± 22.0	8.5 ± 5.8	−7.1
Sarin et al. 2004	34	106	63	6	18.9 ± 17.1	9.7 ± 6.7	−9.3
Sachs et al. 2006	37	136	50	3	20.3	7.8	−.5
Potkin et al 2003	39	202	69	4	12.4	5.9	−6.5
Hanssens et al. 2008	43	150	74	6	33.4	5.2	−28.2
Chen et al. 2011	48	9	100	16	26.5 ± 17.0	3.7 ± 1.9	−22.8

66.4% had subnormal (≤2 ng.mL) PRL endpoint levels. In the five studies with means and a pooled SD, the children receiving ARI treatment ($n = 507$) had a weighted endpoint PRL mean of 1.6 ± 2.1 ng/mL. In this group, 57.1% had ARI endpoint PRL serum levels ≤2 ng/mL.

A composite PRL serum level analysis

The composite weighted mean and SD of the PRL serum levels from the 15 studies reporting baseline norms from healthy populations and from psychiatrically ill children (total $n = 1203$) was 7.3 ± 3.9 ng.mL (Table 1). In this population, a composite 8.3% had subnormal serum levels of PRL (≤2 ng/mL) at baseline. In the ARI-treated children from the 11 pediatric clinical trials ($n = 706$), the composite endpoint PRL serum level weighted mean and SD was 1.7 ± 2.1 ng/mL (Table 2). Of those so treated, 59.7% had PRL serum levels ≤2 ng/mL. Therefore, 60% of children <13 years of age who had been administered ARI developed subnormal PRL serum levels compared with 8.3% who were untreated.

Impact of ARI on PRL levels in adults

Table 3 presents changes in PRL serum levels in chronically ill psychiatric adults who were treated with ARI but had been previously treated – often for years – with other antipsychotic medications (e.g., Sarin et al. 2004; Lee et al. 2010). A number of these studies included inpatients, and in some there was no medication washout or only a very brief one before switching to ARI (Sachs et al. 2006; Hanssens et al. 2008; Chen et al. 2011). Following treatment with ARI, serum PRL levels for the great majority dropped to within the normal range (between 4 and 10 ng/mL; Table 3). but none reported subnormal PRL levels. Similarly, in a study of healthy adults given ARI to measure its impact on PRL levels, it was found that the PRL level decreased from 11.3 ng/mL to within the lower portion of the normal range (to ∼4 ng/mL) (Mallikaarjun et al. 2004).

Impact of ARI on PRL levels of adolescents

In two large ARI clinical trials in adolescents, the reduction of PRL by ARI to abnormally low serum levels (<3ng/mL in females and <2 ng/mL in males) was reported to affect 30% whose mean age was 13.5 years ($n = 197$) and 32% whose mean age was 15.5 years ($n = 202$) (Findling et al. 2008a, 2009b). These studies of adolescents reported a smaller percentage of subnormal PRL serum levels following ARI treatment (30–32%) compared with that for children (60%).

Impact of duration and dose of ARI on PRL

It is of note that the response of PRL to ARI is rapid, appearing within the first week (Musil et al. 2009). With extended ARI treatment, there is a tendency for PRL serum levels to further decline. This is true for both youth (Marcus et al. 2011; Findling et al. 2012) and adults (Mallikaarjun et al. 2004; Vieta et al. 2005; Shim et al. 2007; Yasui-Furukori et al. 2010). Likewise in children, with increasing doses of ARI, there is a dose-dependent decline in PRL serum levels (Findling et al. 2008a, b, Zhang 2008; Findling et al. 2009a; Marcus et al. 2009; Zhang 2009).

Discussion

The major findings in this review pertain to age differences in PRL serum levels following treatment with ARI. The data presented indicate that after treatment with ARI, 60% of children responded with subnormal levels of PRL compared with 30–32% of adolescents. No clinical trials with ARI in adults reported subnormal levels of PRL, but in a major adult reference norm, ∼2–3% of adults had subnormal baseline serum PRL levels; these being at or below two standard deviations from the mean (Siemens 2012).

In psychiatrically ill children entering clinical trials and in reference norms of children, their baseline prevalence of subnormal PRL serum levels averaged 8.3%. In two placebo-controlled trials in adolescents, 2.4% (Findling et al. 2009b) and 8.0% (Findling et al. 2008a) who received a placebo had subnormal PRL serum levels. In reference norms listing 95% central PRL serum level ranges of children 4–12 years of age ($n = 1214$), the average PRL level of those at the 2.5th percentile was 2.4 ng/mL (Cook et al. 1992; Wiedemann and Jonetz–Mentzel 1993; Soldin et al. 1995; Gassler et al. 2000; Beltran et al. 2008; Aldrimer et al. 2012). Using the data from Tables 1 and 2, ARI-treated children exhibited a sevenfold greater rate of subnormal PRL serum levels (60% vs. 8%) than did unmedicated children. Using the placebo rates and the data from other reference norms on subnormal PRL levels in unmedicated children as reported, the comparative degree to which ARI induces subnormal PRL levels in children appears even greater than sevenfold.

Variations in PRL levels by age and sex

PRL serum levels in unmedicated male adults average 7 ng/mL (Friesen and Hwang 1973; Meltzer et al. 1974; Gruen et al. 1978; Siemens 2012). PRL serum levels are similar between male and female children, mildly higher in adolescents than in children, similar in adolescents as in adults, and generally higher in women of menstrual age (averaging 10–12 ng/mL) than in adult men (Friesen and Hwang 1973; Cook et al. 1992; Siemens 2012). Adolescent females in most laboratory norms have mildly higher PRL levels than do adolescent males (Wiedemann et al. 1993; Wudarsky et al. 1999; Alfaro et al. 2002).

Variations in drug-induced PRL sensitivity by age

In response to antipsychotic medications such as olanzapine, risperidone and quetiapine, youth experience greater increases in serum PRL levels than do adults (Wudarsky et al. 1999; Kinon et al. 2003; Alfaro et al. 2002; Becker and Epperson 2006; Migliardi et al. 2009; Paing et al. 2011; Cookson et al. 2012). In contrast, after treatment with ARI, youth experience a far greater rate of subnormal PRL levels than do adults, as shown herein

It is not clear what developmental processes account for the increased sensitivity of children to different antipsychotic agents influencing PRL release. This may be related to the maturation of central dopaminergic signaling. This research, however, is complicated by inconsistent findings across different species (Goldman-Rakic and Brown 1982; Seeman et al. 1987; Rinne et al. 1990). Furthermore, whereas the brain D1and D2 receptors in the caudate nucleus and the putamen decline from the neonatal period to late adulthood (Rinne et al. 1990), there are related findings on D1 and D2 receptor protein levels and on dopaminergic markers in the prefrontal cortex that are not consistent with this (Weickert et al. 2007; Rothmond et al. 2012). Therefore, the increased sensitivity of children to changes in PRL serum level remains to be clarified by further research

An additional factor that may alter PRL secretion is the sex steroid milieu, particularly regarding estrogen, which has both direct and indirect effects on pituitary PRL synthesis and the PRL response to various stimuli (Freeman et al. 2000). Finally, the stress of venipuncture may transiently elevate serum PRL, especially in individuals with anxiety or ''needle phobia.'' This may be a particular problem in establishing a normal range for serum PRL in healthy children who are not accustomed to venipuncture.

What is missing in the medical literature?

What is also missing from the literature is a better understanding of the potential developmental sequelae of subnormal PRL levels. Similarly, it is not known whether *in utero* exposure to ARI has any impact on fetal development.

Limitations

This review is limited by the unavailability of PRL-related detailed data in several studies in children, adolescents, and adults. Nonetheless, using statistical adjustments for incomplete data, consistent PRL findings have emerged. Whereas procedures for PRL serum measurements have been standardized for nearly 30 years (Schuster et al. 1989; Beltran et al. 2008), a few baseline PRL assays in this report still appear to be unexpectedly elevated (e.g., Ercan et al. 2012). The use of means and SDs exclusively for the age group analyses of PRL levels is a limitation in that most of the reference norms are in medians. However, it should be noted that for children, the medians and means have similar distributions. It is possible that differences in PRL levels could be influenced by the underlying psychiatric condition, although no evidence of this was found in two studies (Friesen and Hwang 1973; Gruen et al. 1978).

Conclusions

This review aimed to quantify – in ARI-treated children – the reduction of PRL levels to subnormal levels and to evaluate its impact. We found that the decline in PRL levels is age and dose dependent and is most prominent in children <13 years of age. However, the clinical significance of this hormonal change remains to be determined.

Disclosures

No competing financial interests exist.

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