Some Effects of Risperidone and Quetiapine on Growth Parameters and Hormone Levels in Young Pigtail Macaques

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Abstract

Objective: Atypical antipsychotic drugs are prescribed to young children for a number of symptoms, some with no Food and Drug Administration approval for children. Effects on growth of children have received little experimental study. We assessed the effects of two atypicals, risperidone and quetiapine, on growth, prolactin, and thyroid hormones of young pigtail macaques (*macaca nemestrina*), modeling potential effects on 4–8-year-old children.

Methods: Subjects were studied blindly after random assignment to risperidone ($N = 10$), quetiapine ($N = 10$), or placebo ($N = 20$). Four phases were studied: (1) predrug, 9–12 months of age; (2) low dose (risperidone 0.025 mg/kg, quetiapine 2 mg/kg), 13–16 months; (3) high dose (risperidone 0.05 mg/kg, quetiapine 4 mg/kg), 17–20 months; (4) postdrug, 21–24 months. Body weight was measured daily, skeletal dimension monthly, and bone mineralization and hormones bimonthly.

Results: Our primary result showed that, compared with placebo, neither drug had detrimental effects on body weight, skeletal dimensions, or thyroid hormones. However, in a transient effect, bone density was lower following low-dose risperidone than either quetiapine or placebo. In both drug phases, risperidone prolactin was higher than the other groups, which did not differ. The higher prolactin of the risperidone group may partially explain the bone density effect.

Conclusion: This 16-month study of young, developing pigtail macaques given risperidone at doses from 0.025 to 0.05 mg/kg or quetiapine at doses from 2 to 4 mg/kg suggests that these drugs are safe for normal body weight and skeletal growth in young pigtail macaques given an adequate diet, although these drugs are known to cause significant weight gain and other metabolic changes in some children, adolescents, and adult humans. In addition, the results, although transient in our study, also suggest that research in children on bone mineralization effects of risperidone, and possibly other antipsychotic drugs, may be warranted.

Introduction

ATYPICAL ANTIPSYCHOTIC DRUGS are prescribed to young children for symptoms of autistic disorder, conduct disorder, attention-deficit/hyperactivity, and psychotic and mood disorders (Olsson et al. 2006). Conservative estimates suggest that up to 30% of the market share of this class of drugs is derived from pediatric prescriptions. The majority of these agents have been approved by the Food and Drug Administration (FDA) for older children and adolescents, but not for younger children under 8–10 years of age, being given “off-label.” However, risperidone does have FDA approval for some indications in children within these age groups. Sedation and dizziness are commonly reported adverse effects of these agents as a class. However, class warnings of an increased risk

of weight gain, weight-related metabolic alterations (e.g., insulin resistance and hyperlipidemias), and tardive dyskinesia confer a high risk for later medical consequences of long-term use. As a drug class, data on young children concerning effects on normal development, fertility, carcinogenesis, or mutagenesis are limited (Jensen et al. 2007; Vitiello et al. 2009). Typical antipsychotics such as chlorpromazine and haloperidol have been studied in children, and clinical trials identify neurotoxic effects even at low doses.

The atypical drug risperidone has FDA approval in children and adolescents for irritability in autism, acute schizophrenia, and bipolar disorders. High-dose effects are comparable to typical antipsychotics in producing high-affinity binding to dopamine receptors, leading to extrapyramidal symptoms and hyperprolactinemia (Trugay et al. 2002; Findling et al. 2003). Although no

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This study was supported by NIH grants MH064647 to G. Sackett, RR00166 to the Washington National Primate Research Center, and HD02774 to the University of Washington Center on Human Development and Disability.

evidence of skeletal growth abnormalities has been reported, studies typically included only older children and young adolescents. Excessive weight gain is often reported, but two recent studies showed that not all children or adolescents exhibit it. Fraguas et al. (2008) found excessive weight gain in only 50% of 66 patients and Haas et al. (2009) found somewhat higher, but not excessive, weight gain for 106 adolescents treated with risperidone compared with placebo. Quetiapine, the most widely prescribed atypical, is approved in adults for treatment of schizophrenia, bipolar disorder, and major depression. It has not been approved for any disorder in children. Its lower binding affinity to dopamine receptors is associated with a lower incidence of extrapyramidal symptoms and hyperprolactinemia. Otherwise, it carries similar safety risks associated with the atypical class of drugs. Its safety profile in people below 18 years old has received little testing. We compared both drugs with placebo for effects on growth, prolactin, and thyroid hormones.

Our study was designed to provide comparative indices of safety for children by studying a normally developing primate model (9–24-month-old pigtail macaques, *macaca nemestrina*) with comparable sensory and cognitive developmental ages to 4–8-year-old children (e.g., Diamond 2006). For macaque monkeys, this age range is well before the onset of puberty and a large adolescent growth spurt, which typically occurs between 3.5 and 4.5 years of age. We predicted that during chronic treatment, risperidone will produce a dose-related greater increase in weight gain relative to placebo controls, whereas quetiapine will produce a dose-related decrease in bone growth not seen with risperidone and intermediate weight gain. Quetiapine was not expected to affect ponderal growth based on its pharmacology and the doses employed. Suppression of bone mineralization in quetiapine animals was expected secondary to quetiapine suppression of thyroid function and inhibition of bone calcium deposition found in other animal models. Although delayed skeletal maturation could also occur with risperidone as a result of prolactin elevation, intermediate nondose-dependent effects were expected.

Materials and Methods

Subjects and rearing

All procedures were approved by the University of Washington Institutional Animal Care and Use Committee. We studied 40 male pigtail macaques (*macaca nemestrina*) reared by their mothers in ¼-acre outdoor corrals at the Tulane National Primate Research Center, Covington, Louisiana. Corral groups contained 2–4 breeding males and 15–25 females and their infants. At 6–7 months of age, infants were shipped to the Washington National Primate Center Infant Primate Laboratory (IPRL) in Seattle. Infants arrived in cohorts of five, all within 30 postnatal days of age. They were adapted to cage living and standard lab husbandry for feeding, cage cleaning, and health assessments (Ruppenthal and Sackett 1992) for the next 5–6 months. Although individually housed with visual and auditory access to other monkeys, all received 30–45 minutes of daily peer socialization in playroom groups throughout the study.

Measures

Body weight was measured daily and skeletal dimensions were taken at the end of each month using instruments designed to measure macaque body lengths and widths. Bone mineral density (BMD) and bone mineral concentration (BMC) were measured by dual-energy X-ray absorptiometer at the end of months 1 and 3 of

each of the four study phases defined below. Animals were anesthetized by ketamine for 30–45 minutes during skeletal and dual-energy X-ray absorptiometer sessions. Prolactin and thyroxine (T4) were assayed at the University of Washington Department of Laboratory Medicine as part of a blood chemistry panel. During each study phase, animals received a great deal of physical and psychological interaction with humans during husbandry, behavioral testing, and the growth measures of this study, all standard methods used in the IPRL, described in detail at http://depts.washington.edu/iprl/iprl_testing.html.

Group assignment and dosing

During a 4-month predrug phase from 9 to 12 months old, all animals received the placebo condition. This was a daily 7:00 a.m. butterscotch flavored liquid treat delivered by syringe. Animals were then randomly assigned to a risperidone, quetiapine ($n = 10$ for each), or placebo group ($n = 20$) and studied in three 4-month phases: low dose (risperidone 0.025 mg/kg, quetiapine 2.0 mg/kg), high dose (drug subjects switched to risperidone 0.05 mg/kg, quetiapine 4 mg/kg), and postdrug. Placebo was given to all animals during weeks 1–2 of the postdrug phase, and then all treats were discontinued. These dose levels are in the low-to-moderate dose equivalence by body weight for children (e.g., Fraguas et al. 2008; Haas et al. 2009).

At the end of month 12, prior to the start of drug treatment, one animal was removed from each of the 10 cohorts, resulting in four animals per cohort group. This was done so that any animal exhibiting abnormal physical, health, or behavioral development could be removed from the study. Three cohorts had an animal removed for abnormalities. A randomly chosen animal was removed in the remaining seven cohorts. Each cohort was assigned to a random schedule of risperidone or quetiapine. Within each cohort, two animals were randomly assigned to the drug and the other two received placebo. Drug doses were added to the placebo solution. Placebo and/or drug doses were delivered daily between 6:45 and 7:15 a.m. during phases 1–3 of the study. Age at the start of the study did not differ significantly between drug groups, although the quetiapine group was older than the other two by an average of 12–15 days. Cohorts of four animals were used because this is a standard group size for our laboratory protocol playroom socialization procedure. Because of a need of sufficient time each day to perform all study procedures and personnel limitations, we could only test three to four cohorts at a time. The total study took 54 months for completion. Figures 1–4 illustrate the four phases by 4 months-in-phase design of the study. All personnel involved in testing or husbandry were blind to the experimental condition of the subjects.

Results

Growth

Data were analyzed by repeated measure analyses of variance within each phase, studying month and drug main effects, and the drug $\times$ month interaction. Means and standard errors are shown in Figure 1. Mean monthly body weight (panel A) had a linear increase in each phase for each group (all $p < 0.001$), with no significant drug main or interaction effects (all $p > 0.25$). Three skeletal dimension measures (head circumference, panel B1; foot length, B2; crown-rump length, B3) also increased in each phase for all groups (all $p < 0.001$). Although no drug or interaction effect was significant in any phase (all $p > 0.20$), the risperidone head circumference was lower than that of the other groups from high

FIG. 1. Body weight by drug group, study phase, and month within phase. SEM = standard error of the mean.

dose month 3 onward, but was not significantly different from the other groups at any of these months (all $p > 0.05$ by t -tests). BMD (panel C1) and BMC (C2) generally increased over the course of the study (all $p < 0.01$). However, in the low-dose condition there was a significant drug ($p = 0.017$) and drug $\times$ month interaction ($p = 0.006$) produced by lower bone density in the risperidone group. Risperidone also had lower bone density during the postdrug phase, but neither the drug nor drug $\times$ month effect was significant (both $p > 0.10$). BMC development was similar to BMD (lower

risperidone in the low-dose and postdrug phases) but no drug or interaction effect was significant (all $p > 0.10$).

Prolactin and T4

Prolactin and T4 (free T4, thyroid stimulating hormone, and T4) were measured at the end of predrug, end of months 1 and 3 of each drug phase, and end of postdrug month 1. The results for prolactin are shown in Figure 2. All differences at each month during the

FIG. 2. Skeletal development by drug group, study phase, and month within phase. Upper graph: head circumference (HC); middle graph: foot length (FL); lower graph: crown-rump length (CRL). SEM = standard error of the mean.

FIG. 3. Bone mineralization by drug group, study phase, and month within phase. Upper graph: bone mineral concentration (BMC); lower graph: bone mineral density (BMD). SEM = standard error of the mean.

low- and high-dose phases between risperidone and each of the other two groups showed $p < 0.001$ by Bonferroni tests. No differences were significant between quetiapine and placebo at either dose, and no differences between any of the drug groups were significant in the pre- or postdrug phases (all Bonferroni $p > 0.25$). As in studies with humans (Findling et al. 2003), monkeys given risperidone had markedly elevated prolactin by the end of month 1 of the low-dose phase. Risperidone group prolactin remained elevated, but with a gradual decline, during the low- and high-dose phases. Prolactin returned to placebo levels by the end of the first postdrug month. Quetiapine did not produce elevated prolactin relative to placebo during any phase of the study.

Risperidone had a slightly higher free T4 level than the other two groups ($p = 0.02$) at the end of the predrug phase. However, thereafter there were no significant thyroid measure group or group $\times$ month effects during any phase or at any month tested (all $p > 0.10$).

Discussion

Both risperidone and quetiapine appear to be safe in our study with respect to body weight and skeletal dimensions. Although we ex-

pected higher body weight in risperidone-treated subjects, this was not found. Studies by Sikich et al. (2008) and Correll et al. (2009) did find excessive weight gain with risperidone or quetiapine in children. However, the participants in both studies were much older on average than those in our study, most being near or into adolescence. Our subjects were 1–2 years younger than the 3.5–4 years age typical of puberty onset and an accompanying growth spurt in male macaque monkeys. Other findings of no excessive weight gain in many young children treated with risperidone (Fraguas et al. 2008; Haas et al. 2009) suggest that our result is not too surprising. Also, our adequate but not excessive monkey chow diet, supplemented with fruits and vegetables, does not lend itself to overeating or excessive caloric intake. An adequate diet may not be found for many children under antipsychotic drug treatment, which could be one reason for excessive weight gain due to excessive intake when on a drug regimen. Findings of excessive weight gain in first-world country studies may as likely be due to excessive intake as antipsychotic agents. However, an adequate diet in terms of caloric limits and nutritional balance may not be found for many children treated with antipsychotic drugs, so our results may not apply to either macaques or children on nutritionally poor diets.

FIG. 4. Prolactin development by drug group, study phase, and month within phase.

TABLE 1. PEARSON PRODUCT MOMENT CORRELATIONS AND ONE-TAILED PROBABILITY LEVELS BETWEEN BONE MINERAL DENSITY AND PROLACTIN BY PHASE AND MONTH IN PHASE (N = 40)

	<i>Predrug</i>		<i>Low dose</i>		<i>High dose</i>		<i>Postdrug</i>
	<i>M3</i>	<i>M1</i>	<i>M3</i>	<i>M1</i>	<i>M3</i>	<i>M1</i>	
Prolactin							
R	0.24	−0.38	−0.29	−0.18	−0.12	−0.18	
Probability	0.072	0.008	0.033	0.135	0.231	0.226	

Our results do caution that bone mineralization may be diminished by risperidone. Elevated prolactin has been postulated, but not proven, to produce bone density deficiencies in adult humans (Abraham et al. 2003) and prolactin was elevated by risperidone throughout the dosing period in our study. However, this stimulatory effect of risperidone on prolactin levels did decrease somewhat over time, a phenomenon also observed in humans (Findling et al. 2003). The attenuation of the differences in bone density, both over time and despite higher risperidone dosages, may possibly have been mitigated as a result of a partial recovery of posterior pituitary function from risperidone-mediated dopamine receptor blockade. Also a mechanism such as compensatory mineralization due to higher growth or sex hormone levels prior to the juvenile growth spurt may have occurred at our high-dose phase in these risperidone-treated male macaques. Some support for a relationship between bone density and prolactin is shown in Table 1. Bone density and prolactin were significantly, but not strongly, negatively correlated during the low-dose phase. Nonsignificant negative correlation occurred thereafter, as might be expected from the lack of a risperidone bone density effect after the low-dose phase. These transient, complicated, developmental effects require replication and further study for full understanding.

Conclusions

This 16-month study of young, developing pigtail macaques given risperidone at doses from 0.025 to 0.05 mg/kg or quetiapine at doses from 2 to 4 mg/kg suggests that these drugs are safe for normal body weight and skeletal growth in young pigtail macaques given an adequate diet, although these drugs are known to cause significant weight gain and other metabolic changes in some children, adolescents, and adult humans. In addition, the results, although transient in our study, also suggest that research in children on bone mineralization effects of risperidone, and possibly other antipsychotic drugs, may be warranted.

Disclosures

The authors Sackett and Crouthamel have no conflicts of interest. The author Unis was employed from 2001 to 2003 by Johnson & Johnson Pharmaceutical Research and Development, LLC, and worked on the pediatric exclusivity research related to the development of risperidone. However, the primate study for this publication was developed before his employment and the data collection was completed after his employment ended. Risperidone is currently off patent and no commercial interests are served by the results of the present research. Unis is a speaker for Janssen Pharmaceuticals, Inc., but risperidone is no longer promoted by this company since its patent expired.

Acknowledgments

The authors thank Laura Newell-Morris for consultation and training on anthropometric measurement, and Sarah Ward, Rebecca Warren, Erika Rainwater, and Caroline Kenney for data collection.

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