Predictors of Risperidone and 9-Hydroxyrisperidone Serum Concentration in Children and Adolescents

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Abstract

Introduction: Little is known about risperidone metabolism in a clinical sample, where polypharmacy is common. Such knowledge is important since several of its side effects are dose dependent.

Methods: Medically healthy patients aged 7 to 17 years old treated with risperidone for at least 6 months were enrolled. Trough serum risperidone and 9-hydroxyrisperidone concentrations were measured.

Results: One hundred seven participants (92% males) were recruited, representing a heterogeneous clinical group with attention-deficit/hyperactivity disorder, disruptive behavior disorders, pervasive developmental disorders, anxiety disorders, mood disorders, tic disorders, or psychotic disorders. Risperidone had been used at a mean dose of 0.03 mg/kg, for a mean 2.5 years, predominantly to treat irritability and aggression. Cytochrome CYP2D6 inhibitors were divided into prominent (fluoxetine, bupropion, and lamotrigine), intermediate (sertraline), and weak inhibition groups (citalopram or escitalopram). The concentrations of risperidone and its metabolite were strongly associated with the dose of risperidone and time since the last dose and, to a lesser extent, with male sex. In addition, risperidone concentration increased with pubertal stage ($p < 0.05$), while body mass index z -score ($p = 0.001$) predicted a higher 9-hydroxyrisperidone concentration. The use of CYP2D6 inhibitors was much more strongly associated with risperidone concentration ($p < 0.0001$) than with its metabolite's ($p = 0.06$).

Conclusions: In chronically treated youths, the metabolism of risperidone depends on the stage of sexual development, whereas that of 9-hydroxyrisperidone varies with body fat. Moreover, CYP2D6 inhibitors more strongly affect risperidone metabolism than that of its metabolite. The clinical implications of these findings, in relation to efficacy and tolerability, deserve further investigation.

Introduction

RISPERIDONE IS A widely used antipsychotic in children and adolescents. It has received FDA labeling for pediatric mania, schizophrenia, and irritability in autistic disorder (FDA 2006, 2007). It has also been found efficacious in the treatment of tic disorders, disruptive behavior disorders, and attention-deficit/hyperactivity disorder (Aman et al. 2002, 2004; Dion et al. 2002). Like other medications, however, risperidone causes adverse events, a number of which appear to be dependent on the dose or serum concentration. For instance, in children and adolescents, prolactin concentration is closely associated with the oral dose of risperidone and its serum concentration (Casaer et al. 1994; Calarge et al. 2009a), and weight gain is dose related (Correll et al. 2009).

The pharmacokinetic characteristics of risperidone have been thoroughly examined in several studies in adults, but few investigations have involved children and adolescents, despite extensive use in this population. After oral ingestion, risperidone is rapidly absorbed and reaches a maximum concentration in the serum in ~1 hour (Heykants et al. 1994). It is extensively metabolized in the

liver, mainly through 9-hydroxylation by the CYP2D6 enzyme, generating 9-hydroxyrisperidone (Huang et al. 1993). This equipotent metabolite has comparable receptor binding profile to the parent drug (Huang et al. 1993; Heykants et al. 1994; van Beijsterveldt et al. 1994). Therefore, the combined risperidone and 9-hydroxyrisperidone serum concentration is often used to estimate the circulating active moiety. However, risperidone and 9-hydroxyrisperidone do not necessarily have the same tissue distribution. In fact, the brain-to-plasma concentration ratio is higher for risperidone than for its metabolite while the opposite is true in the kidneys and the liver (van Beijsterveldt et al. 1994; Aravagiri et al. 1998). This difference can have potential clinical implications in terms of efficacy and tolerability.

Although the pharmacokinetics of risperidone are not affected by age (Casaer et al. 1994; Aman et al. 2007), its half-life varies depending on the activity of the CYP2D6 enzyme. The majority of Caucasians are extensive metabolizers, but ethnic and racial variability exists (Bradford 2002). In addition, this inherited metabolic activity could be significantly altered by medications. In fact, among psychotropics, commonly used antidepressants and anti-convulsants are potent modulators of CYP2D6 activity (de Leon

et al. 2005). By inhibiting this enzyme in the gut wall and the liver, these medications will enhance the fraction of risperidone absorbed in the portal circulation and deliver a higher fraction of the parent drug to the systemic circulation, respectively. Therefore, the impact of concomitantly prescribed psychotropics on risperidone metabolism in youths may be of clinical significance particularly since polypharmacy is prevalent (Safer et al. 2003; dosReis et al. 2005; Zito et al. 2008).

Thus, taking advantage of a sizeable sample of children and adolescents recruited in a study evaluating the long-term safety of risperidone (Calarge et al. 2010), we set out to identify potential predictors of risperidone and 9-hydroxyrisperidone serum concentrations. Since co-administered medications could influence the serum concentrations of risperidone and its active metabolite, which, in turn, may affect tolerability, and since the tissue distribution differs between the two drugs, such investigation could inform clinical care.

Participants and Methods

The rationale, design, and primary aims of the original study have been described elsewhere (Calarge et al. 2009a, 2010). Briefly, 7- to 17-year-old participants, treated with risperidone for 6 months or more, were enrolled in a study examining the long-term effect of risperidone on metabolic, hormonal, and skeletal outcomes. Youths with serious medical or neurological disorders were excluded as were pregnant women and those receiving hormonal contraception.

The psychiatric diagnoses and treatment history were obtained from the medical record. After an overnight fast ($n = 100$, 93%), a blood sample was obtained in the morning ($n = 100$, 93%) to measure a trough risperidone and 9-hydroxyrisperidone serum concentrations using liquid chromatography/tandem mass spectrometry. The coefficient of variation was 8.84% for risperidone and 13.5% for its metabolite and the detection limit for both was 0.5 ng/mL. Seven (7%) participants could not fast. They ate between 2 and 5.75 hours before the blood draw. In four of these same participants, the blood sample was obtained in early afternoon, the latest being by 14:40. Also, two of the nonfasting participants, in addition to another five for a total of 7 (7%), could not have their morning dose of risperidone withheld until after the blood draw. Instead, they received their medication between 1.15 and 5.75 hours beforehand. Excluding those participants who could not fast and those who received their morning dose of risperidone did not alter the results substantially, except where noted. Upon recruitment, the daily dose of risperidone and the time of the last dose were documented. Pubertal status was determined by physical examination or self-assessment, using a locally developed and validated form consisting of age-appropriate instructions and pictures depicting Tanner stages I through V (Marshall and Tanner 1969, 1970; Calarge et al. 2010). Height and weight were measured following standard procedures, and body mass index (BMI) was computed as weight (kg) divided by height squared (m^2) (Calarge et al. 2010). Using the CDC database, the gender- and age-adjusted z -scores were generated (Ogden et al. 2002).

This study was approved by the local Institutional Review Board. Assent was obtained from children ≤ 14 years old and consent from adolescents and parents or guardians.

Statistical analysis

The serum concentrations of risperidone, its metabolite, and the active moiety were log transformed to normalize the data

residuals. Multiple linear regression was used to model each, with the following covariates: Pubertal stage, sex, BMI z -score, weight-adjusted daily dose of risperidone (mg/kg/day), time since risperidone was last ingested (hours), total duration of risperidone treatment (years), and concomitant use of CYP2D6 inhibitors. The latter was categorized in four mutually exclusive groups based on the use of medications with incremental inhibitory activity. Group 1 included those concomitantly treated with citalopram ($n = 7$, 7%) or escitalopram ($n = 6$, 6%), group 2 included those treated with sertraline ($n = 10$, 9%), and group 3 included those treated with fluoxetine ($n = 30$, 28%), bupropion ($n = 2$, 2%), or lamotrigine ($n = 1$, 1%) (de Leon et al. 2005). The fourth group (group 0) included those not taking any of these medications ($n = 51$, 48%). The listed covariates were selected because we were particularly interested in exploring any potential effect of development and sex on risperidone metabolism. In addition, due to the differential tissue distribution of risperidone and its metabolite, we wondered whether ponderosity also influenced their clearance. At enrollment, no one was receiving fluvoxamine, paroxetine,azole antifungal medications, calcium channel blockers, cimetidine, macrolide antibiotics, phenytoin, propoxyphene, rifampin, or tramadol, medications that are reported to modulate CYP2D6 enzyme activity. Only one patient received carbamazepine concomitantly (excluding this participant did not alter the findings appreciably). Neither psychostimulants nor α_2 -agonists modulate CYP2D6 enzyme activity (Beckett and Shenoy 1973; Boehringer-Ingelheim 2006; Shire 2009a, 2009b). Finally, to provide a clinically useful estimate of the differential impact of the four CYP2D6 inhibitor groups on risperidone-related concentrations, we computed a Cohen's d effect size.

All the analyses were two-tailed and conducted using SAS version 9.2 for Windows (SAS Institute Inc., Cary, NC).

Results

Sample characteristics

A total of 107 participants had complete data and were included in the analysis. Table 1 lists the demographic and clinical characteristics of the sample. Most were pre- or peri-pubertal, non-Hispanic white boys, and suffered from an externalizing disorder, though comorbidity was prevalent with 93% ($n = 99$) of the sample carrying two or more clinical diagnoses (Table 1). Two of the youths smoked: One lightly (< 1 cigarette/day) and the other smoked a pack per day. Risperidone was predominantly used to treat irritability and aggression associated with disruptive behavior disorders or pervasive developmental disorders (FDA 2006; Pliszka et al. 2006), at a dose consistent with the published literature (Aman et al. 2002). By enrollment, the participants had been on risperidone for a mean duration of 2.5 years ($sd = 1.7$) and on their current dose for a mean of 0.8 year ($sd = 0.9$). Only seven children received risperidone monotherapy. In fact the median number of psychotropics taken, in addition to risperidone, was 2.0 (interquartile range: 1.0). The most common concomitant medications included psychostimulants, selective serotonin reuptake inhibitors (SSRIs), and α_2 -agonists. Of note, more than half the sample (52%) received psychotropics that can inhibit the CYP2D6 enzyme.

As noted earlier, we aimed to measure the trough serum concentration of risperidone and its metabolite. Thus, we instructed the participants not to take their morning dose of risperidone on the day of the blood draw. In fact, the median interval between the last dose of risperidone and the blood draw was 14.1 hours (interquartile

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE

Characteristic	Mean or n	SD or %
Age, years	11.4	2.8
Males	98	92
Tanner stage: I, II, III, IV, V	46/18/18/19/6	43/17/17/18/6
Race		
Non-Hispanic white	88	82
African American	10	9
Hispanic	5	5
Other	4	4
Cigarette smoking	2	2
Body mass index z-score	0.6	1.1
Psychiatric diagnoses		
Attention-deficit/hyperactivity disorder	92	86
Disruptive behavior disorder	69	65
Anxiety disorder	40	37
Depressive disorder	21	20
Tic disorder	21	20
Pervasive developmental disorder	13	12
Psychotic disorder	2	2
Risperidone dose, mg/kg/d	0.03	0.03
Risperidone level, ng/mL ^a	4.8	6.1
9-Hydroxyrisperidone level, ng/mL	8.2	9.7
Active moiety level, ng/mL	11.2	12.5
Indication for risperidone		
Irritability/aggression	88	82
Tics	10	9
Resistant ADHD	6	6
Sleep problems	2	2
Impulse control disorder	1	1
Concomitant medications		
Risperidone only	7	7
Stimulants	76	71
SSRIs	54	50
α_2 -agonists	34	32
CYP2D6 inhibition groups ^b		
Group 0	51	48
Group 1	13	12
Group 2	10	9
Group 3	33	31

^aThis includes only the 67 patients whose risperidone serum concentration was above the detection limit of the assay.

^bCYP2D6 inhibition groups consisted of those not taking a CYP2D6 inhibitor (group 0), those taking citalopram or escitalopram (group 1), those taking sertraline (group 2), and those taking fluoxetine, bupropion, or lamotrigine (group 3).

ADHD = attention-deficit/hyperactivity disorder; SSRIs = selective serotonin reuptake inhibitors.

range: 3.2). In 40 individuals, risperidone serum concentration was undetectable, whereas that of its metabolite was above the detection limit of the assay. In the total sample, risperidone concentration represented around a quarter of the serum level of the active moiety (mean = 24%, sd = 24) with the concentration of 9-hydroxyrisperidone forming the rest.

As shown in Table 2, multiple linear regression analysis revealed that risperidone serum concentration was significantly associated with pubertal development, the weight-adjusted dose of risperidone, time since the last dose was ingested, and the concomitant

use of CYP2D6 inhibitors ($p < 0.0001$). In addition, there was a trend for males to have a higher risperidone concentration. This model accounted for 55% of the variance in risperidone serum concentration. Compared with those not taking any inhibitors (group 0), those in groups 1 and 3 had higher (log transformed) risperidone serum concentration (Cohen's $d = 0.68$, $p < 0.05$ and Cohen's $d = 1.65$, $p < 0.0001$, respectively) (Fig. 1). Receiving sertraline (group 2) was associated with a lower risperidone serum concentration compared to both groups 1 and 3 (Cohen's $d = 0.91$, $p < 0.04$ and Cohen's $d = 1.88$, $p < 0.0001$, respectively) but not group 0 (Cohen's $d = 0.23$, $p > 0.5$). Finally, risperidone serum concentration was lower in those treated with citalopram or escitalopram (group 1) compared to group 3 (Cohen's $d = 0.97$, $p < 0.006$). Overall, the CYP2D6 inhibitors group explained 28% of the variance in risperidone serum concentration. On the other hand, neither BMI z-score nor the total duration of risperidone treatment significantly associated with it. Restricting the analysis to males did not appreciably alter the results. However, when we excluded those participants who could not fast and those who received their dose of risperidone in the morning, the association of male sex with higher risperidone concentration became significant ($\beta = 1.19$, se = 0.48, $p < 0.02$).

9-Hydroxyrisperidone serum concentration (log transformed) was associated with a different, although overlapping, set of predictors (Table 2). In fact, neither the stage of sexual development nor the duration of risperidone treatment were significantly related to it. However, being a male, BMI z-score, and the weight-adjusted dose of risperidone were positively associated with the metabolite concentration with time since risperidone was last administered being negatively correlated with it. The concomitant use of CYP2D6 inhibitors failed to significantly predict 9-hydroxyrisperidone concentration ($p = 0.06$). In fact, it only explained 2.9% of the variance in the metabolite concentration, whereas the total model accounted for 64%. More specifically, only a few differences between the four CYP2D6 inhibitors groups were apparent. Participants concomitantly treated with sertraline (group 2) had a higher concentration of the metabolite (log transformed) compared to those in groups 0 and 3 (Cohen's $d = 0.73$, $p < 0.05$ and Cohen's $d = 0.89$, $p < 0.02$, respectively) (Fig. 1). Comparable findings resulted when we restricted the analysis to boys though the association between the use of CYP2D6 inhibitors, and 9-hydroxyrisperidone concentration was statistically significant ($p < 0.03$). In fact, boys using citalopram, escitalopram, or sertraline (groups 1 and 2) had higher 9-hydroxyrisperidone concentrations compared to those in groups 0 and 3.

Finally, while pubertal development was not associated with the concentration of the active moiety, being a male led to a higher level (Table 2). In addition, the serum concentration increased with ponderosity, the use of CYP2D6 inhibitors, and receiving a higher weight-adjusted dose of risperidone. It decreased with longer intervals between the last administration of risperidone and the blood draw. The duration of risperidone treatment was not associated with the serum concentration of the active moiety. Although the concentration of the active moiety gradually increased as more potent CYP2D6 inhibitors were used ($p < 0.03$), *post-hoc* analyses testing the effect of the inhibitor groups on the concentration revealed that the difference was significant only between those not taking any inhibitors and those in group 3 (Cohen's $d = 0.68$, $p < 0.004$) (Fig. 1). This overall model accounted for 70% of the variance in the serum concentration of the active moiety with the CYP2D6 inhibitor groups accounting for

TABLE 2. MULTIPLE LINEAR REGRESSION MODELS PREDICTING SERUM CONCENTRATION OF RISPERIDONE, ITS METABOLITE, AND THE ACTIVE MOIETY IN CHILDREN AND ADOLESCENTS

	Predictor variable	β estimates	SE	t	p Value
Risperidone	Tanner stage	0.22	0.11	2.04	<0.05
	Sex (male)	0.81	0.45	1.80	<0.08
	BMI z-score ^a	0.01	0.11	0.85	>0.3
	Risperidone dose (mg/kg/day)	18.60	5.34	3.49	0.0007
	Time of risperidone intake (hours)	-0.10	0.02	-5.03	<0.0001
	Risperidone treatment duration (years)	0.09	0.08	1.10	>0.2
	CYP2D6 inhibition groups ^b				
9-Hydroxyrisperidone	Group 1	0.86	0.42	2.06	<0.05
	Group 2	-0.29	0.45	-0.66	>0.5
	Group 3	2.09	0.29	7.23	<0.0001
	Tanner stage	-0.04	0.05	-0.89	>0.3
	Sex (male)	0.42	0.21	2.03	<0.05
	BMI z-score ^a	0.18	0.05	3.38	0.001
	Risperidone dose (mg/kg/day)	22.63	2.48	9.13	<0.0001
	Time of risperidone intake (hours)	-0.04	0.01	-4.67	<0.0001
	Risperidone treatment duration (years)	0.02	0.04	0.58	>0.5
	CYP2D6 inhibition groups ^b				
Active Moiety	Group 1	0.27	0.19	1.38	>0.1
	Group 2	0.43	0.21	2.05	<0.05
	Group 3	-0.10	0.13	-0.73	>0.4
	Tanner stage	-0.01	0.05	-0.15	>0.8
	Sex (male)	0.51	0.19	2.72	<0.008
	BMI z-score ^a	0.17	0.05	3.49	<0.001
	Risperidone dose (mg/kg/day)	22.78	2.24	10.17	<0.0001
	Time of risperidone intake (hours)	-0.06	0.01	-7.29	<0.0001
	Risperidone treatment duration (years)	0.02	0.03	0.69	>0.4
	CYP2D6 inhibition groups ^b				
	Group 1	0.24	0.18	1.39	>0.1
	Group 2	0.29	0.19	1.53	>0.1
	Group 3	0.36	0.12	2.98	<0.004

^aBMI z-score: age- and sex-adjusted body mass index.

^bCYP2D6 inhibition groups consisted of those not taking a CYP2D6 inhibitor (group 0), those taking citalopram or escitalopram (group 1), those taking sertraline (group 2), and those taking fluoxetine, bupropion, or lamotrigine (group 3).

FIG. 1. Least-squares means (error bars = standard errors) of the serum concentration (log transformed) of risperidone, 9-hydroxyrisperidone, and the active moiety, in the four CYP2D6 inhibitor groups, after adjusting for stage of sexual development, sex, weight-adjusted daily dose of risperidone, time interval between the last administration of risperidone and the blood draw, and duration of risperidone treatment. CYP2D6 inhibition groups consisted of those not taking a CYP2D6 inhibitor (group 0), those taking citalopram or escitalopram (group 1), those taking sertraline (group 2), and those taking fluoxetine, bupropion, or lamotrigine (group 3).

3% of it. The results did not change appreciably when girls were excluded from the analysis.

Discussion

To our knowledge, this is the largest study to identify predictors of risperidone metabolism in a pediatric sample. Risperidone is widely used in this age group to target a variety of clinical problems (Aman et al. 2002; FDA 2006, 2007). Several of its side effects are dose dependent. However, with polypharmacy being increasingly prevalent in youths (Safer et al. 2003; dosReis et al. 2005; Zito et al. 2008), dose adjustment becomes complicated since little is known about factors that influence its pharmacokinetics in this age group. As would be expected, both the dose and the interval between when it was last ingested and when the blood sample was drawn are key determinants of the serum concentration of risperidone, its metabolite, and the active moiety. However, additional factors, some not having been previously reported, appear to also exert a prominent effect. Some of the factors are shared by both risperidone and its active metabolite, whereas others are unique to each. The fact that the serum concentrations of 9-hydroxyrisperidone and the active moiety are associated with the same set of predictors should come as no surprise since the former composed 76% of the latter in this sample.

Drug metabolism is known to change with age and pubertal development (Hines 2008). However, two pharmacokinetic studies in children with autism have found risperidone clearance somewhat comparable to that in adults (Casaer et al. 1994; Aman et al. 2007). One was small ($n=6$) and involved prepubertal children (age range: 3–7 years) (Casaer et al. 1994), whereas the other was larger ($n=19$) and included children and adolescents (Aman et al. 2007). Interestingly, Aman et al. noted a large inter-individual variability in the concentration–time profiles. They argued that neither dose nor the CYP2D6 metabolizer status (i.e., extensive versus poor) could fully account for this finding (Aman et al. 2007). Their sample size was, likely, too small to allow adjusting for other confounders that proved significant in our sample, including the use of psychotropics that might alter CYP2D6 activity. In fact, only four of their participants took risperidone monotherapy and four actually received, concomitantly, a potent CYP2D6 inhibitor (i.e., fluoxetine, bupropion, or lamotrigine) (Aman et al. 2007). Another methodological difference is that our participants had received risperidone for an extended period (a minimum of 6 months and a mean of 2.5 years), whereas other studies assessed risperidone pharmacokinetics either following a single dose or after 1 week of starting treatment (Casaer et al. 1994; Aichhorn et al. 2007; Aman et al. 2007). To what extent these factors could have led to the divergence in the findings is not clear.

In the first year of life, hepatic CYP2D6 and CYP3A4 activity almost reach the levels observed in adults (Blake et al. 2007; Johnson et al. 2008; Stevens et al. 2008). Thus, the positive association we found between pubertal status and risperidone concentration is unlikely to be due to a change in the activity of these CYP enzymes during development. Rather, our finding might reflect a difference, across the Tanner stages, in the dose of CYP2D6 inhibitors taken concomitantly. For example, the dose of selective serotonin reuptake inhibitors, received by our participants, significantly increased with pubertal development ($p < 0.0002$). This would further attenuate the CYP2D6 enzyme activity and, consequently, increase risperidone serum concentration. While we did account for the use of CYP2D6 inhibitors in the analyses, we could not adjust for the dose due to the variety of psychotropics involved.

As anticipated, the serum concentration of risperidone was strongly associated with the potency of psychotropics to inhibit the CYP2D6 enzyme (de Leon et al. 2005). Thus, the concentration was highest in those receiving a potent inhibitor, such as fluoxetine (group 3), followed by those receiving citalopram and escitalopram (group 1). It is unclear why sertraline was associated with a concentration no different than those not receiving CYP2D6 inhibitors (group 0). The age, sex distribution, and concomitant medications used in sertraline-treated youths appeared similar to those in the other three groups (data not shown). It is possible that the potential of sertraline to inhibit CYP2D6 is a weak one, with little detectable effect on risperidone metabolism (Alfaro et al. 2000; Liston et al. 2002). The influence of the medications in group 1 or 3 on risperidone concentration might have clinical implications if risperidone and its active metabolite are differentially associated with efficacy or tolerability but also because taking a CYP2D6 inhibitor led to a higher concentration of the active moiety, though this was only statistically significant for group 3. Although 9-hydroxyrisperidone is primarily eliminated by the kidneys, unchanged (Samtani et al. 2009), a significant proportion is further metabolized by CYP2D6. In fact, the co-administration of paroxetine, a potent CYP2D6 inhibitor, increased paliperidone concentration by 16% in extensive metabolizers (Ortho-McNeil-Janssen Pharmaceuticals 2007). This is consistent with our finding of a positive, although small, association between the use of CYP2D6 inhibitors and the serum concentration of the metabolite.

In this study, after adjusting for potential confounders, including the weight-adjusted dose of risperidone, sex accounted for around 2% in the variance of risperidone, 9-hydroxyrisperidone, and the active moiety, with boys having higher serum concentrations. That risperidone is more slowly metabolized in males is consistent with evidence of a higher CYP2D6 activity in women (Hagg et al. 2001). Its metabolite, on the other hand, is predominantly eliminated by the kidneys, as noted earlier (Samtani et al. 2009). However, by 2 years of age, glomerular filtration rate reaches adult levels, adjusting for body surface area, and is no different in young males and females (Kon and Ichikawa 2004; Rule et al. 2004). Thus, it is likely that the sex effect we found is due to a differential clearance of 9-hydroxyrisperidone through other, though less prominent, sex-dependent routes such as further metabolism by CYP2D6 (Ortho-McNeil-Janssen Pharmaceuticals 2007). Our findings, however, contrast with those of Aichhorn et al., who reported that females had higher serum concentrations (Aichhorn et al. 2007). Yet, in their study, which included a significantly smaller sample of youths treated with risperidone, they do not control for the use of CYP2D6 inhibitors or some of the other confounders we considered. In addition, they measured risperidone levels 7 days after the onset of treatment and all their participants had been hospitalized upon enrollment. On the other hand, it is conceivable that the girls in our outpatient group were less adherent to the prescribed medication due to adverse events they are more susceptible to, such as hyperprolactinemia and its sequelae (Calarge et al. 2009a).

After accounting for several covariates, including the weight-adjusted dose, the age- and sex-adjusted BMI z -score accounted for a significant share of the variance in 9-hydroxyrisperidone and the active moiety but not of risperidone. To our knowledge, a differential distribution of risperidone and its active metabolite to the adipose tissue has not been established. This, however, is possible in light of evidence showing a higher metabolite to risperidone concentration ratio in the liver and kidneys, whereas the opposite is true in the brain (van Beijsterveldt et al. 1994; Aravagiri et al. 1998). Apparently, in the first month of treatment with intramus-

cular paliperidone palmitate, the concentration of 9-hydroxyrisperidone was higher in lean adults than in those with a BMI $>25 \text{ kg/m}^2$ (Samtani et al. 2009). With sustained treatment, however, this association disappeared, suggesting that it was primarily due to a difference in the uptake of the drug from the injection site. This, however, is not relevant to orally administered drugs. The implications of our finding on tolerability and efficacy are unclear but should be investigated since risperidone, like other atypical antipsychotics, is associated with a substantial increase in fat mass in youths (Calarge et al. 2009b; Correll et al. 2009). Thus, over time, as excessive weight accumulates, the serum concentration of 9-hydroxyrisperidone and the active moiety will increase, perhaps resulting in improved efficacy but also in a higher rate of adverse events. The possible development of a vicious circle of increased ponderosity promoting the accumulation of 9-hydroxyrisperidone in turn leading to more weight gain deserves further investigation.

Our findings should be interpreted in light of the study limitations. First, all of our participants were living in the community. Thus, medication adherence could not be guaranteed. Nevertheless, we verified it by asking the parents, reviewing the medical records, and, in most cases, reviewing pharmacy records. Further, the participants had been in treatment with risperidone for an average of 2.5 years. Whether the same predictors are associated with more acute treatment is unclear but likely since the duration of risperidone treatment was not associated with any of the outcomes of interest. The majority of our participants were taking other psychotropics, in addition to risperidone, with more than half taking a medication that specifically interferes with its metabolism. Therefore, our results might not fully apply to a same-age population treated only with risperidone. Such children, however, represent the minority since polypharmacy is prevalent (Safer et al. 2003; dos-Reis et al. 2005; Zito et al. 2008). In addition, though the sample is relatively large, smaller subgroups resulted when we divided the participants based on the concomitant use of CYP2D6 inhibitors, possibly reducing statistical power to conduct some of the *post-hoc* analyses. Our models accounted for 55% to 70% of the variance in the outcomes of interest. However, the prediction of the models could have possibly further improved had we genotyped the CYP2D6 gene. More than 70 variants have been identified, and the genotype–phenotype correspondence has not been fully established (Zhou 2009). In addition, there appears to be a complex effect of race that we also could not account for due to the under-representation of minority groups in our sample (Bradford 2002; Gaedigk et al. 2002; Gaedigk et al. 2007). Finally, the role of P-glycoprotein in regulating the brain transport of risperidone, 9-hydroxyrisperidone, as well as a number of other psychotropics is increasingly recognized as is the potential for its activity to be modulated by these drugs (Wang et al. 2006; Zhu et al. 2007). Thus, the extent to which P-glycoprotein contributes to the variability in the disposition of risperidone and its metabolite and how this might affect clinical outcomes require further clarification.

Conclusions

In sum, as expected, we found that the dose of risperidone and the time since its last administration were significantly associated with the serum concentration. However, some of the psychotropics most often prescribed concomitantly with risperidone slow its metabolism with gender and pubertal development also exerting an effect. Finally, a possible association between fat mass and 9-hydroxyrisperidone concentration might explain why some adverse events, like weight gain (Calarge et al. 2009b), take months to years

to plateau. It has been argued that the influence exerted by CYP2D6 enzyme activity on risperidone metabolism is of limited clinical significance since the serum concentration of the active moiety is little affected (Heykants et al. 1994). However, more studies are necessary to evaluate if CYP2D6 enzyme inhibition of risperidone metabolism is beneficial, particularly if treatment response is positively associated with serum concentration. Alternatively, it may be problematic if the risperidone to metabolite ratio influences clinical efficacy or if adverse events, resulting from an increased serum concentration, prohibit tolerability.

Disclosure Statement

Chadi Albert Calarge and Del D. Miller have no conflicts of interest or financial ties to disclose.

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