Paliperidone Palmitate in a Child with Autistic Disorder

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To the Editor:

AUTISTIC DISORDER (AUTISM) is a neuropsychiatric disorder characterized by impairments in social interaction, communication, and stereotyped behaviors and interests (American Psychiatric Association 2000). Individuals with this disorder often exhibit associated interfering symptoms including irritability, hyperactivity, and inattention. Irritability, defined as aggression, severe tantrums, and self-injury, is a particularly limiting symptom with the capacity to diminish the quality of life for both the affected individual and their caregivers.

Historically, antipsychotics have been the pharmacologic treatment of choice for irritability in youth with autism. Early research focused on typical antipsychotics such as haloperidol (Cohen et al. 1980; Anderson et al. 1984). Atypical antipsychotics have a lower rate of side effects such as dyskinesias and are currently considered first-line choice for treatment of irritability associated with autistic disorder (Erickson et al. 2007; Blankenship et al. 2010). Both risperidone and aripiprazole were approved by the U.S. Food and Drug Administration (FDA) to treat irritability in youth with autism aged 5–16 and 6–17 years, respectively. Multiple double-blind, placebo-controlled studies have demonstrated the efficacy of risperidone (Research Units on Pediatric Psychopharmacology Autism 2002; Shea et al. 2004) and aripiprazole (Marcus et al. 2009; Owen et al. 2009) for the treatment of this symptom domain.

Paliperidone is the active metabolite of risperidone and was approved by FDA to treat schizophrenia and schizoaffective disorder in adults. Stigler et al. (2010) recently described the effectiveness of paliperidone in treating irritability in two individuals with autism. A 16-year-old female patient and a 20-year-old male patient, both diagnosed with autism, were treated with paliperidone (3 and 12 mg/day, respectively) after they demonstrated a lack of adequate improvement on other medication regimens. Both were judged to have significant improvement in their symptoms, including aggression and tantrums, with paliperidone treatment. No adverse events were reported. Both individuals lost weight and experienced improvements in their fasting lipid profiles while taking paliperidone.

In 2009, the FDA approved a sustained-release intramuscular (IM) formulation of paliperidone, paliperidone palmitate, for the treatment of adults with schizophrenia. In this report, we demonstrate the successful use of paliperidone palmitate for the treatment

of irritability in a child with autism who was unable to tolerate oral medications.

Materials and Methods

B is a 5-year-old boy diagnosed with autistic disorder by a board-certified child and adolescent psychiatrist (C.J.M.) using *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision criteria (DSM-IV-TR) (American Psychiatric Association 2000). B has a history of intense irritability including aggressive behavior and frequent severe tantrums. He was often violent with others, and on one occasion, he fractured his caregiver's nose. B was initially treated with trials of risperidone and aripiprazole administered in both tablet and liquid oral formulations (maximum daily dosages of 1 and 2 mg, respectively), resulting in a noticeable decrease in aggression and tantrums. However, B developed a significant aversion to all forms of oral medication administration. His primary caregiver attempted a variety of techniques to encourage B to ingest medications, including placing the drugs in favorite foods and manually assisting B to swallow medications. Although difficult to clearly determine, B's refusal of oral medications appeared to be oppositional in nature, rather than due to a sensory issue or adverse effect.

B's refusal of medications became overwhelming to his caregivers and had led to discontinuation of all psychotropics. Off psychotropic medications, B's behavior continued to be severe and disruptive, limiting his ability to participate in family life and academics. The unrelenting nature of his behavior and his consistent refusal to take medications in a variety of forms led to the consideration of an IM depot form of medication.

Paliperidone palmitate, the IM formulation of paliperidone, was discussed as a potential treatment option with B's caregivers. This medication is typically delivered through an injection deep into the deltoid muscle and is dosed on a monthly basis to maintain steady state of the medication at a therapeutic level. The depot formulation of risperidone was considered initially because of B's history of positive response to this medication. However, risperidone requires twice monthly dosing, creating greater stress for B and his caregivers. In preparation for administration of paliperidone palmitate, an oral test dose of paliperidone 1.5 mg tablets was prescribed. Through extreme means, his caregiver was able to administer three doses, which B tolerated without adverse effect. Treatment was

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This work was supported by a National Institutes of Health grant KL2 UL1 RR025761 and Indiana University Clinical and Translational Sciences Institute Career Development Award (to Dr. Erickson); The Division of Disability and Rehabilitative Services, Indiana Family and Social Services Administration (to Drs. Erickson, Wink, and McDougale); Daniel X. and Mary Freedman Fellowship in Academic Psychiatry (to Dr. Stigler); NIMH grant K23 MH082119 (to Dr. Stigler); and NIMH grants R01 MH072964, R01 MH077600, and R01 MH083739 (to Dr. McDougale).

then initiated with paliperidone palmitate at 39 mg/0.25 mL, which is the smallest IM dose available. No loading dose was given. Informed consent was obtained from B's primary caregiver, following discussion of the off-label usage of this medication. The medication was prescribed by B's psychiatrist at our institution, but was administered at his primary care physician's office at the request of the family to ease travel concerns. B received 39 mg/0.25 mL paliperidone palmitate IM monthly for 3 months.

Results

Results were obtained from subjective reports by B's mother at 3 months following initiation of treatment and from pre- (retrospective) and posttreatment Aberrant Behavior Checklist (ABC) scores, Clinical Global Impressions (CGI) Severity Scale (CGI-S) scores, and CGI Improvement Scale (CGI-I) scores (Guy 1976; Aman et al. 1985). The ABC is an informant-based scale comprised of the following five subscales: irritability, lethargy, stereotypy, hyperactivity, and inappropriate speech. The CGI-S measures illness relative to the patient's previous visit on a scale from 1 to 7, with 1 being "not ill" and 7 equivalent to "extremely ill." In this report, the CGI-I focused on the target symptoms of irritability and was rated from 1 to 7, with 1 equal to "very much improved" and 7 equal to "very much worse."

Approximately 3 months following initiation of paliperidone palmitate, B demonstrated remarkable improvement. His aggression and tantrums had diminished in frequency and severity. His primary caregiver reported improved concentration and reported that B was more compliant with instructions. At the 3-month follow-up visit, B's primary caregiver completed the ABC for both pre- (retrospective) and posttreatment with paliperidone palmitate. Improvement was noted on four of the five subscales (Table 1). On the CGI-S at baseline, B was given a score of 6 or "severely ill" and a score of 2 or "minimally ill" after 3 months of treatment. Given his level of clinical improvement in irritability, B was assigned a CGI-I score of 1 or "very much improved" at his 3-month follow-up appointment.

Paliperidone palmitate was well tolerated. B's caregiver reported an increase in appetite as the only notable adverse effect. There was no reported difficulty with administration of the medication. During the 3 months of treatment, B's body mass index rose from 16.4 to 19.2. He did not develop abnormal motor movements or other evidence of extrapyramidal symptoms.

TABLE 1. COMPARISON OF B'S SCORES ON THE ABERRANT BEHAVIOR CHECKLIST PRE- AND POSTTREATMENT WITH PALIPERIDONE PALMITATE

<i>Aberrant Behavior Checklist subscale</i>	<i>Pretreatment with paliperidone palmitate</i>	<i>Posttreatment with paliperidone palmitate</i>	<i>% Change</i>
Irritability	34	13	-62
Lethargy	21	4	-81
Stereotypy	12	5	-58
Hyperactivity	45	18	-60
Inappropriate speech	0	0	0

Subscale maximum scores: Irritability = 45, lethargy = 48, stereotypy = 21, hyperactivity = 48, inappropriate speech = 12.

Discussion

This case reports on our experience with paliperidone palmitate in a 5-year-old boy with autism and irritability. This child was significantly limited by the severity of his behaviors and was unable to effectively take oral medication. Since initiation of treatment with paliperidone palmitate, his global level of irritability has significantly decreased. B has gained weight since initiation of treatment, with an increase in his body mass index. He did not develop other significant adverse reactions to the medication.

Clinical Implications

Although this report is limited by size, the uncontrolled nature of the investigation, and the retrospective administration of the baseline ABC, the results are compelling. To date, oral risperidone and aripiprazole are the mainstays of treatment of irritability in children with autism, but there are cases in which an alternative delivery method may be necessary. The use of paliperidone palmitate in this case suggests a possible treatment option for children unable to tolerate oral administration of medications.

Disclosures

Dr. Erickson is on Scientific Advisory Boards and receives research grant support from Seaside Therapeutics, F. Hoffmann-LaRoche, and Novartis. Dr. McDougle is on the Speakers Bureau for and receives research support from Bristol-Myers Squibb Co. Dr. Stigler receives research support from Janssen, Bristol-Myers Squibb Co., and Forest Pharmaceuticals. Dr. Kowalski, Dr. Wink, Dr. Blankenship, and Ms. Habenicht have no disclosures.

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