Abstract

Objective: The aim of this study was to report preliminary data on the effectiveness and tolerability of ramelteon for the treatment of insomnia in youth with autistic disorder (autism).

Method: Two youths, ages 7 and 18 years, with autism and significant insomnia characterized by problems with sleep onset and maintenance received an open-label trial of ramelteon (4–8 mg) over a duration of 16–18 weeks.

Results: Target symptoms of delayed sleep onset and/or frequent nocturnal awakening improved significantly, as determined by Clinical Global Impressions-Improvement (CGI-I) scale ratings of either “much improved” or “very much improved.” Ramelteon was well tolerated. No daytime sedation was reported.

Conclusions: This case report illustrates the potential effectiveness and tolerability of ramelteon for sleep disturbances in 2 patients with autism. Further research is needed to verify its safety, tolerability, and efficacy in children and adolescents with autism.

Introduction

Autistic disorder (autism) is a life-long neuropsychiatric disorder characterized by marked impairments in social interaction, communication, and repetitive interests and activities (American Psychiatric Association 2000). Maladaptive symptoms, such as aggression, self-injurious behavior, agitation, and hyperactivity are frequently observed (Stigler et al. 2002). In addition, significant difficulties with sleep have been reported (Tiara et al. 1998; Richdale 1999; Honomichl et al. 2002). Sleep disturbances are observed, on average, in two-thirds of youths with autism (Richdale 2001). Sleep onset and maintenance are the areas usually affected, and they often begin early in these youths and can remain a problem for years (Hoshino et al. 1984; Patzold et al. 1998; Tiara et al. 1998; Paavonen et al. 2003). In contrast, parasomnias, such as nightmares, sleepwalking, or sleep talking, do not appear to be increased in this population (Richdale 1999). As a whole, these interfering symptoms are often overwhelming to the affected youths and their families.

To date, sleep has been investigated in autism via several modalities, including surveys, polysomnography, actigraphy, and sleep diaries. Hering and colleagues (1999) reported that 12 (54.5%) of 22 parents surveyed endorsed abnormal sleep patterns in their children, including difficulties with sleep onset and maintenance. Results from sleep diaries and the Children’s Sleep Habits Questionnaire (CSHQ) of 100 youth with autism and related disorders found that all subjects had longer sleep onset times and greater fragmentation of sleep despite initial parental perceptions indicating otherwise (Honomichl et al. 2002). More recently, sleep problems were evaluated via a parent survey in 53 children with autism, 52 children with Asperger’s disorder, and 66 normal control youths (Polimeni et al. 2005). Sleep problems were common in all groups, with significantly more problems reported in the autism (73%) and Asperger’s disorder (73%) groups.

In regard to measuring sleep, polysomnography is considered the “gold standard” (Malow 2004). A polysomnographic study was undertaken in 17 children and adolescents with autism, 7 patients with mental retardation and fragile X syndrome, and 5 normal controls (Elia et al. 2000). The authors found a significant reduction in total sleep time in the individuals with autism versus the controls. Another polysomnographic study revealed a sleep efficiency index (percentage of total sleep time/time in bed) of 81% in 10 autistic subjects versus 92% in 8 normal controls (Diomedi et al. 1999).

The treatment of insomnia often begins with behavioral interventions (Lancioni et al. 1999). These sleep hygiene methods generally involve the use of a fixed schedule for sleep and wake times, with sleep outside of these times minimized or eliminated if possible. Implementing a nightly routine is also often helpful. Although behavioral approaches are often beneficial, medication may be required to manage the severe insomnia frequently observed in individuals with autism. To date, little research into the pharmacotherapy of sleep disturbances has been conducted in this population.

Melatonin (MT) is a hormone produced from serotonin in the pineal gland and is considered to play an important role in regulating human circadian rhythms (Tordjman et al. 2005). This is of interest given that serotonergic dysfunction has been documented in autism by many investigators (McDougle et al. 2005). In addition, a lower mean concentration of MT and abnormal circadian secretion of the hormone have been reported in blood samples from individuals with autism (Nir et al. 1995; Kulman et al. 2000). More recently, nocturnal MT secretion was found to be significantly lower in 49 youths with autism in comparison to 88 matched normal controls (Tordjman et al. 2005). The excretion rate was negatively correlated with impairment in verbal communication and play.

The use of MT for insomnia was described in a case report of an adolescent with Asperger’s disorder (Horrigan and...
Barnhill 1997). Treatment with MT (3 mg) improved sleep maintenance, academic performance, and afternoon alertness. MT (6 mg) improved the sleep-wake rhythm and prolonged night sleep in an adolescent with autism (Hayashi 2000). A 2-week, open-label trial of MT (3 mg) in 15 youths ages 6–17 years with Asperger’s disorder and sleep disturbance found improvement in the sleep patterns of all subjects, with half demonstrating an excellent response. Because of the possible relationship between sleep problems and disruptive daytime behavior (Wiggs and Stores 1996; Corkum et al. 1998), behavioral measures were obtained. These measures showed a significant improvement in anxiety, withdrawal, and aggression. Overall, the drug was well tolerated. One child withdrew due to excessive sedation, dizziness, and diarrhea.

Ramelteon, a MT receptor agonist, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with insomnia characterized by delayed sleep onset. The drug has high affinities for the MT1 and MT2 receptors, with affinities up to 16 times higher than those of MT (Kato et al. 2005). These receptors are implicated in the regulation of sleepiness and the sleep–wake cycle (Erman et al. 2006). Ramelteon is metabolized primarily via the cytochrome p-450 (CYP) 1A2, and to a lesser degree by CYP 2C and 3A4. No abuse potential or rebound insomnia has been reported with the drug. Large double-blind, placebo-controlled studies in adults with insomnia have demonstrated ramelteon to be effective in decreasing sleep latency (Roth et al. 2005) and increasing total sleep time (Erman et al. 2006). The drug was well tolerated, with headache, somnolence, and pharyngitis among the adverse effects reported. There were no next-day residual effects.

In this report, we describe our clinical experience with ramelteon in the first 2 autistic patients we treated. It was hypothesized that ramelteon would be well tolerated and efficacious for the treatment of delayed sleep onset in this population.

**Methods**

The sample consisted of 2 male youth ages 7 and 18 years with autism. Diagnoses were made with the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision* (DSM-IV-TR) (American Psychiatric Association 2000) by a child and adolescent psychiatrist (K.A.S.). The parents of each patient gave informed consent for treatment within the Christian Sarkine Autism Treatment Center at the Indiana University School of Medicine. Both patients were receiving concomitant psychotropic medications, which were continued at the same dosage during treatment with the drug. Large double-blind, placebo-controlled studies in adults with insomnia have demonstrated ramelteon to be effective in decreasing sleep latency (Roth et al. 2005) and increasing total sleep time (Erman et al. 2006). The drug was well tolerated, with headache, somnolence, and pharyngitis among the adverse effects reported. There were no next-day residual effects.

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**Results**

**Case 1**

A is a 7-year-old African-American male who presented for an initial evaluation at 5 years of age. A developmental history found that A has struggled with significant impairment in social skills. This has included decreased eye contact, lack of imaginative play, absence of joint attention, and a preference for solitary activities. A’s adoptive mother reported that he used one word at 2 years of age, but has been nonverbal since that time. In addition, he engaged in repetitive interests and activities, including spinning objects and pacing in circles. He tended to function best with a routine in place. A’s history and presentation supported a DSM-IV-TR diagnosis of autism; in addition, he had moderate mental retardation based on history and testing.

A has a history of severe interfering behaviors consisting of self-injury aggression, property destruction, and hyperactivity. Significant insomnia was also of concern. Prior medication trials for aggression and repetitive behavior included risperidone, sertraline, guanfacine, and clonidine. Currently, A receives olanzapine for interfering symptoms of aggression at a dosage of 5 mg every morning and afternoon, and 10 mg nightly. Despite this treatment, he continued to exhibit significant insomnia on a nightly basis, involving a delay in sleep onset of 2–3 hours, as well as frequent awakening during the night. Implementing behavioral measures to target the insomnia were unsuccessful. Previous medication trials for interfering behavior, which included nightly doses of risperidone, guanfacine, and clonidine, did not alleviate the insomnia. A prior trial of trazodone was reported ineffective, and A exhibited a paradoxical response to diphenhydramine, primarily consisting of agitation.

After discussion, it was decided to initiate a trial of ramelteon at 4 mg nightly in an effort to target the insomnia. Olanzapine was continued at the same dosage during treatment with ramelteon. A’s mother reported significant improvement in both sleep onset and maintenance immediately after starting the drug. However, the child continued to exhibit difficulties with sleep 3–4 nights per week, with a delayed sleep onset of approximately 1 hour and brief frequent awakening. Thus, after 4 weeks, ramelteon was increased to 8 mg nightly to further target these symptoms. A follow-up report after 16 weeks found that symptoms of insomnia had further improved. With a sleep onset of approximately 25 minutes, A was no longer having problems initiating sleep. Furthermore, the brief intermittent awakening only occurred one to two times weekly. He was deemed “much improved,” as determined by a CGI-I score of 2. Ramelteon was well tolerated, without any residual day-time sedation.

**Case 2**

B is an 18-year-old Caucasian male referred for diagnostic clarification and medication management. A detailed developmental history revealed that B had difficulties with social interaction that involved poor eye contact and joint attention skills, as well as a preference for solitary activities. He has not developed peer relationships. Language development was delayed, with B saying his first word at 2 years of age. Echolalia and pronoun reversal were also endorsed. Repetitive interests and activities have included a fascination with fans and cars. Routine has been important to his overall well being. B’s level
of intellectual functioning has been judged to fall into the range of moderate mental retardation. In addition to this diagnosis, he met DSM-IV-TR criteria for autism.

B’s mother reported a history of significant disruptive behaviors, including aggression, self-injury, and hyperactivity. In addition, B exhibited a delay in sleep onset lasting up to 3 hours per night. This sleep disturbance persisted during psychotropic medication trials aimed at targeting the interfering behaviors. Past medication trials included sertraline, fluoxetine, methylphenidate, risperidone, gabapentin, paroxetine, olanzapine, quetiapine, and aripiprazole. Nightly doses of the atypical antipsychotic drugs, as well as dipherhydramine at a maximum dosage of 75 mg nightly were ineffective for disturbed sleep. B currently is prescribed clonidine 0.05 mg every morning and noon and 0.1 mg after school, valproic acid 250 mg twice daily, paroxetine 5 mg each morning, and methylphenidate 20 mg three times daily. Although behavior was well controlled, the insomnia continued.

Ramelteon was added at a dosage of 4 mg nightly. B’s psychotropic medications were continued at the same dosage during the ramelteon trial. Three days after initiating the drug, B’s difficulties with sleep onset had resolved. Sleep onset had decreased to approximately 20 minutes. The benefits have been maintained over the past 18 weeks. B was judged to be “very much improved” and assigned a CGI-I score of 1. No adverse effects have occurred during treatment with ramelteon, including any residual daytime sleepiness.

Discussion
This case report illustrates our clinical experience with ramelteon in the first 2 youths with autism whom we treated. Both patients were considered responders as determined by a CGI-I rating of “much improved” or “very much improved.” Difficulties with delayed sleep onset were resolved. Furthermore, 1 patient who experienced additional problems with sleep maintenance demonstrated an improvement in sleep continuity. The drug’s effectiveness was maintained in these patients over a duration of 16 and 18 weeks, respectively.

Ramelteon was very well tolerated. No residual daytime sedation was reported. In addition, none of the commonly reported adverse effects associated with ramelteon, including headaches, somnolence, dizziness, or fatigue, was observed in the 2 youths. The tolerability described in this report may be secondary to the drug’s receptor profile. Ramelteon has negligible affinity for other receptor binding sites in the central nervous system, including benzodiazepine, opioid, muscarinic, histamine, and γ-aminobutyric acid (GABA) (Kato et al. 2005). In addition, its relatively short half-life of 1.2 hours likely contributed to the lack of daytime sedation observed in the 2 youths.

Insomnia is commonly observed in youths with autism. In light of research to date that suggests abnormalities in blood levels and circadian secretion of MT, ramelteon’s mechanism of action as a highly selective MT1 and MT2 receptor agonist may contribute toward its effectiveness and tolerability in this diagnostic group. That MT has been found beneficial in the treatment of insomnia in individuals with autism and related disorders suggests that ramelteon, a more potent drug, may play an important role in the treatment of severe sleep disturbances in this population. Although improvement was documented in sleep onset and maintenance in this small sample, additional research is needed to clarify the drug’s effectiveness for these symptoms.

In contrast to other pharmacological agents indicated for the treatment of insomnia in adults, ramelteon has not been associated with cognitive impairment, abuse, or rebound insomnia. In children and adolescents, psychotropic drugs such as atypical antipsychotics, antidepressants, or α-2 adrenergic agonists are also often used to target insomnia. The potential adverse effects associated with these drugs, including weight gain, tardive dyskinesia, extrapyramidal symptoms, and hypotension, may outweigh their benefits. Although continued experience will elucidate its tolerability profile, ramelteon may be considered ideal for youths with autism and severe sleep disturbances. Further study is needed to determine any potential long-term effects of this drug in developing youth.

This case report has several significant shortcomings that limit the reliability and validity of these findings. Treatment with ramelteon was conducted in an unblinded and uncontrolled fashion. In addition, the report involves only 2 subjects over a relatively short duration of treatment. Although diagnoses were made by a child and adolescent psychiatrist experienced in the diagnosis and treatment of autism and related disorders, a standardized diagnostic instrument, such as the Autism Diagnostic Inventory–Revised (Lord et al. 1994) was not used. Importantly, prospective measures often employed in studies involving sleep onset and maintenance, such as sleep diaries and actigraphy, were not incorporated into this assessment. The subjects described were also limited in their ability to articulate subjective adverse effects, given their level of intellectual functioning and language development.

Despite these limitations, this report provides initial clinical information on the treatment of sleep disturbances in 2 youths with autism. Our early experience suggests that ramelteon may prove to be an effective and well tolerated treatment for severe insomnia in some children and adolescents with autism and related disorders. Controlled research is needed to determine the efficacy and tolerability of ramelteon in this diagnostic group.

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