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Original Article

Management of Excessive Daytime Sleepiness in Narcolepsy With Baclofen

Anne M. Morse, DO [a, b], Kristin Kelly-Pieper, MD [c, d], Sanjeev V. Kothare, MD [d, e, f, *]

[a] Department of Child Neurology, Geisinger Medical Center, Janet Weis Children's Hospital, Danville, Pennsylvania
[b] Department of Sleep Medicine, Geisinger Medical Center, Janet Weis Children's Hospital, Danville, Pennsylvania
[c] Division of Pediatric Pulmonology and Cystic Fibrosis Center, Cohen Children's Medical Center, Lake Success, New York
[d] Pediatric Neurology Service Line for Northwell Health, Department of Pediatrics & Neurology, Zucker School of Medicine at Hofstra/Northwell, Cohen Children's Medical Center, Lake Success, New York
[e] Division of Pediatric Neurology, Department of Pediatrics, Cohen Children's Medical Center, Lake Success, New York
[f] Pediatric Sleep Program (Neurology), Department of Pediatrics, Cohen Children's Medical Center, Lake Success, New York

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ABSTRACT

Background: Narcolepsy is a disabling sleep-wake disorder characterized by the pentad symptoms of excessive daytime sleepiness, sleep paralysis, sleep fragmentation, sleep-related hallucinations, and cataplexy. There is no curative therapy for narcolepsy. Treatment is therefore symptom directed. Symptom management is generally directed at improving excessive daytime sleepiness, sleep fragmentation, and cataplexy. First-line treatment for excessive daytime sleepiness is typically daily use of wake-promoting agents, such as modafinil or armodafinil, or stimulant therapy, such as methylphenidate or amphetamines. Alternatively, sodium oxybate can be used nightly for improved cataplexy, sleep consolidation, and following day wakefulness. These therapies can be limited in some patients because of inadequate efficacy, poor tolerability, or side effects.
Methods: We describe five narcolepsy patients with severe excessive daytime sleepiness who had an inadequate response or experienced side effects with the initial therapies but had a positive response to treatment with baclofen.
Results: These patients reported subjective improvement in sleep maintenance without fragmentation and daytime sleepiness. Average Epworth Sleepiness Scale assessment before treatment was 15.8 with post-treatment assessment being 10.4 ($P < 0.05$).
Conclusions: Baclofen may be an effective treatment for excessive daytime sleepiness and sleep fragmentation in narcolepsy and warrants further study.

Introduction

Narcolepsy is a disabling sleep-wake disorder that typically peaks in onset during the second decade of life[1-3] and has a prevalence of about one in 2000 people.[4] The classic pentad symptoms of narcolepsy include excessive daytime sleepiness (EDS), sleep paralysis, sleep fragmentation, sleep-related hallucinations, and cataplexy. Cataplexy is sudden transient loss of (generalized or focal) tone that is generally provoked by strong emotion, frequently laughter. Patients can have narcolepsy with or without cataplexy. Narcolepsy type 1 is characterized by the presence of severe EDS, symptoms of cataplexy and evidence of orexin (hypocretin) deficiency in the cerebrospinal fluid.[5-7] Narcolepsy type 2 includes patients without cataplexy and normal cerebrospinal fluid orexin levels.[7,8] Narcolepsy is typically diagnosed with night-time polysomnography and following day multiple sleep latency testing, which demonstrates a relatively normal polysomnography with findings of an average sleep latency of less than eight minutes and at least two sleep onset rapid eye movement (REM) periods, which is the presence of REM sleep within the first 15 minutes after sleep onset.[7]

There is currently no cure for narcolepsy. Treatment goals are aimed toward specific symptom relief, which frequently requires polypharmacy. EDS, sleep fragmentation, and cataplexy are typically the symptoms targeted for treatment. First-line therapy

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* Communications should be addressed to: Kothare; Cohen Children's Medical Center; Northwell Health, 2001; Marcus Avenue; Suite W290; Lake Success, NY 11042.
E-mail address: skothare@northwell.edu (S.V. Kothare).

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TABLE.
Patient Clinical Summaries

Patient Demographics	Comorbidities	Diagnostics	Prior Narcolepsy Treatment (Maximum Dosing and Reason for Discontinuation)	Current Narcolepsy Treatment	Epworth Sleepiness Scale Before/After Baclofen
14 years old, female	Anxiety, ADHD	HLA DQB1*0602 positive HLA DR15 positive HLA DQ1*0102 positive PSG: unremarkable MSLT: SL 5.2 minutes; 3 SOREMPs	Sodium oxybate (9 g; nausea, vomiting, weight loss)	Baclofen 30 mg qhs Armodafinil 150 mg Escitalopram 30 mg PM	15/11
15 years old, female	Depression, migraines, thyroid cancer, atypical stereotyped behaviors	HLA DQB1*0602 negative PSG: unremarkable MSLT: SL 3.7 minutes; 4 SOREMPs MRI brain: unremarkable Paraneoplastic studies: negative	Iron, melatonin, armodafinil 150 mg Venlafaxine ER: 150 mg Sodium oxybate (9 g—pregnancy)	Baclofen 40 mg qhs venlafaxine 112.5 mg modafinil 250 mg	18/12
17 years old, male	ADHD, OCD	HLA DQB1*0602 negative PSG: unremarkable MSLT: SL 7.6 minutes; 3 SOREMPs MRI brain: unremarkable FDG PET MRI brain: unremarkable Paraneoplastic studies: negative	Sodium oxybate (12 g—unable to obtain insurance approval) Venlafaxine ER 150 mg AM	Baclofen 40 mg qhs Sodium oxybate 9 g	16/10
13 years old, male	RLS	HLA DQB1*0602 positive PSG AHI 3.4/hour, increased PLMs MSLT: SL 1.3 minutes; 4 SOREMPs EEG: normal MRI brain: unremarkable	Sodium oxybate (9 g—new onset depression) Armodafinil 150 mg AM	Baclofen 25 mg qhs Venlafaxine 75 mg protriptyline 5 mg bid	14/8
16 years old, male	None	HLA DQB1*0602 positive HLA DR15 positive HLA DQA1*0102 positive PSG: fragmented sleep MSLT: SL 2.3 minutes; 4 SOREMPs EEG normal MRI brain: unremarkable	Modafinil 400 mg divided (residual sleepiness) Armodafinil 250 mg qAM (residual sleepiness) Methylphenidate LA 40 mg with methylphenidate IR 10 mg every noon and every 5 pm (arrhythmia)	Armodafinil 250 mg qAM Baclofen 30 mg qhs Planning to try sodium oxybate	16/11

Abbreviations:
ADHD = attention deficit hyperactivity disorder
AHI = Apnea Hypopnea Index
EEG = electroencephalography
ER = extended release
FDG = fluorodeoxyglucose
HLA = human leukocyte antigen
MRI = magnetic resonance imaging
MSLT = multiple sleep latency test
OCD = obsessive-compulsive disorder
PET = positron emission tomography
PLM = periodic limb movements
PSG = polysomnography
qAM = every morning
qhs = nightly
RLS = restless leg syndrome
REM = rapid eye movement sleep
SL = average sleep latency
SOREMPs = sleep onset REM periods

is generally the wake-promoting agents modafinil or armodafinil. Traditional stimulants such as methylphenidate and amphetamines are second and third-line therapies. An alternative treatment for narcolepsy has been sodium oxybate (SO), a gamma-Aminobutyric acid ($GABA_B$) receptor agonist, which was introduced in 2002[9] as a twice nightly medication that helps to consolidate sleep, improve EDS, and reduce cataplectic events.[10] The combination of SO with a wake-promoting agent or traditional stimulant is commonly utilized to maximize wakefulness and daytime performance.[11,12]

Barriers to use of this medication are both medical and logistical. Significant side effects have been reported with SO use, including intense nausea, disruptions in mood and behavior, excessive weight loss, and parasomnias.[13-17] In addition, the expense of the medication can pose a challenging financial burden to families. Finally, the need to obtain SO from a single national distributor requires a significant administrative effort. The combination of these factors makes use of this drug less than optimal.[18,19] Similar to SO, baclofen is a $GABA_B$ receptor agonist,[20,21] raising the question of whether there could be a similar clinical benefit with its use.

We present our experience with five adolescents with narcolepsy type 1 who either failed treatment or experienced intolerable side effects to first-line therapies but whose sleep consolidation and EDS improved with baclofen treatment (Table).

Patient Descriptions

Patient 1

This 14-year-old girl with a history of anxiety and attention-deficit hyperactivity disorder presented after six months of EDS, cataplexy, sleep-related hallucinations, and parasomnias. SO and escitalopram improved cataplexy and EDS; however, she experienced severe nausea, vomiting, and weight loss. After one year, SO was discontinued and armodafinil initiated. She experienced rebound cataplexy and anxiety. SO was restarted with armodafinil and escitalopram. Again, SO was discontinued because of nausea and weight loss. Baclofen was initiated and titrated to 30 mg nightly. EDS significantly improved without impact on cataplexy. Cataplexy was better controlled with higher doses of escitalopram.

Patient 2

This 15-year-old girl with a complex medical history including migraines, depression, atypical stereotyped behaviors, and thyroid cancer presented after two years of EDS and cataplexy. A comprehensive neurological evaluation was performed evaluating for paraneoplastic etiology. SO was poorly tolerated, with increasing atypical behaviors, depression, and a paradoxical insomnia. Increased SO dosing with addition of ferrous sulfate, melatonin, armodafinil, and venlafaxine improved symptoms. Because of pregnancy all medications were discontinued. After delivery, she was started on baclofen and titrated to 40 mg at bedtime, with the addition of venlafaxine and modafinil. Cataplexy and EDS improved with minimal residual symptoms.

Patient 3

This 17-year-old boy with attention-deficit hyperactivity disorder and obsessive-compulsive disorder presented after two years of cyclic episodes of hypersomnia and vivid dreaming He denied cataplexy, sleep paralysis, abnormal eating, or sexual behaviors. SO was initiated with therapeutic benefit at 12 g in three nocturnal divided doses, as he was considered a rapid metabolizer of SO. Dosing was not approved by insurance. Alternatively, baclofen was added to SO 9 g and resulted in improvement of EDS.

Patient 4

This 13-year-old boy with no significant past medical history presented with EDS, cataplexy, vivid violent dreams, and recurrent leg pains since age 10. Venlafaxine, modafinil, and clonidine were initiated with modest benefit. He was subsequently transitioned to SO at 9 g, with addition of armodafinil, and protriptyline and continuation of venlafaxine. Symptoms improved, however, he developed depression after SO initiation, so it was discontinued. He was started on baclofen and titrated to 25 mg at bedtime. He had significant improvement in EDS and cataplexy with baclofen, venlafaxine, and protriptyline.

Patient 5

This 16-year-old boy with no significant past medical history presented at age 13 years after six months of EDS after an Epstein-Barr virus infection. In retrospect he had also experienced episodes of mild cataplexy, but he denied sleep paralysis or sleep-related hallucinations. A combination of long and short acting methylphenidate provided significant relief of EDS. Cataplexy was not treated because of minimal symptoms. At age 15 years, he was discovered to have an asymptomatic arrhythmia temporally related to the doses of stimulant, which were then considered a relative contraindication. He was transitioned to modafinil and later armodafinil and titrated to maximum doses with only modest improvements in EDS. His family was reluctant to start SO at that time. Baclofen was added and titrated to a dose of 30 mg at bedtime. With each dose increase he subjectively noted improved overnight sleep and diminished early daytime symptoms.

Discussion

Narcolepsy is a debilitating condition that can be challenging to manage. Polypharmacy is often required to address the various symptoms, including stimulants, wake-promoting agents, antidepressants, and SO. SO is the only monotherapy treatment that can provide improvement in EDS, fragmented sleep, and cataplexy. The active metabolite in SO is γ-hydroxybutrate (GHB). GHB is a naturally occurring cerebral metabolite,[22] and it is hypothesized to exert its effect on sleep via $GABA_B$ receptor agonism. Physiologically, GHB increases slow wave activity, which is believed to be the relevant mechanism for symptomatic improvement. However, its exact mechanism of action is not known.[23,24]

There are several disadvantages with the use of SO. First, there can be difficulty in obtaining the drug related to a combination of insurance coverage and limited access because of a mandated centralized pharmacy. Second, split night-time dosing can be difficult for patients to manage. Third, the high sodium content of the medication may contribute to development of adverse effects, such as nausea, vomiting, hypertension, and headache. The drug also requires completion of additional Risk Evaluation and Mitigation Strategy program-related forms.

Although there are several alternatives for the treatment of cataplexy and wake promotion, sleep fragmentation is frequently a neglected symptom, especially in pediatric patients, due to discomfort among physicians with the use of hypnotics and to lack of Food and Drug Administration approval for use in this age group. Thus consideration for additional treatments is needed for the pediatric narcolepsy patients.

Baclofen is a centrally acting $GABA_B$ agonist commonly used in pediatrics for treatment of rigidity, spasticity, and dystonia due to a variety of conditions, such as cerebral palsy, poststroke, and multiple sclerosis. In addition, there is evidence that baclofen may provide sleep benefits by reducing sleep latency and increasing slow wave sleep.[25-27] Total sleep time, with both non-REM and REM sleep durations, is also increased, with significant reduction in time spent in wakefulness after sleep onset with baclofen use.[21] In fact, when baclofen and SO were evaluated in healthy volunteers in similar conditions, it was found that most of the sleep and electroencephalography effects found in SO were also present in baclofen; however, there was a delayed onset of action found in baclofen.[28]

In animal studies, significant clinical improvement in both EDS and cataplexy has been observed with the use of R-baclofen. R-baclofen has triple the affinity for the $GABA_B$ receptor compared with S-baclofen.[29] However, R-baclofen is not used clinically. Clinically available baclofen is a racemic mixture, which may account for the variation in clinical response when compared with the use of R-baclofen.

Studies evaluating clinically available baclofen as a treatment for narcolepsy with cataplexy in humans have not shown consistent benefit.[22,30,31] Huang and Guilleminault evaluated the relative response to SO versus baclofen in a cohort of adolescent patients with narcolepsy and cataplexy. Improved total nocturnal sleep was seen in both groups, but no change in daytime sleepiness or cataplexy occurred in patients treated with baclofen. On the other hand, Lee and Douglas[30] and Wierzbicka et al.[31] reported complete to near-complete resolution of cateplexy in adults with narcolepsy and cataplexy who were treated with high dose baclofen.

A variation in response to baclofen treatment may reflect differences in dosing regimen. Huang and Guilleminault[22] used doses of 5 mg to 25 mg nightly, whereas Lee and Douglas[30] and Wierzbicka et al.[31] provided higher doses of 30 mg to 60 mg nightly. On average, our patients were exposed to a higher dose of baclofen and also continued other narcolepsy treatments as part of their regimen. Therefore any beneficial response may reflect the higher dose or possibly synergy with other treatments. Limitations of evaluation of our patients are that repeat multiple sleep latency was not performed in these patients to provide an objective measure of benefit. Patients were aware of the addition of baclofen and placebo effect cannot be excluded. In addition, there was no subjective improvement in cataplexy.

Baclofen is an inexpensive medication with a known safety profile in all ages, facillitating its use as a treatment to increase slow

wave sleep and improve sleep consolidation. Concerns with the use of baclofen include depression, hallucinations, nausea, dizziness, and sensory disturbance.[32] Caution is warranted with higher doses because of the potential lowering of the seizure threshold and the possibility of withdrawal symptoms following abrupt cessation. Rapid withdrawal from baclofen therapy can cause seizures, altered mentation, hallucinations, hyperthermia, and rigidity.[33] Use in individuals with renal impairment can be challenging, because reduced creatinine clearance can lead to the accumulation of baclofen, resulting in additional adverse events. However, there is no manufacturer recommendations for renal dosing.[34]

Future studies should evaluate baclofen at higher dosing with and without other narcolepsy treatments. Repeat sleep studies after initiation of baclofen would provide an objective measure of improvement. Consideration for use of R-baclofen in the treatment of human narcolepsy with cataplexy should be explored for safety and efficacy, as it is proving to be beneficial in animal models.

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