Off-Label Treatment of Severe Childhood Narcolepsy-Cataplexy With Sodium Oxybate

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Study Objectives: To evaluate the efficacy and side-effect profile of off-label sodium oxybate (gamma hydroxy butyrate) therapy in severe childhood narcolepsy-cataplexy.

Design: Retrospective; chart review.

Setting: A multidisciplinary tertiary sleep center.

Patients: A group of eight children with severe narcolepsy-cataplexy diagnosed on the basis of clinical history, nocturnal polysomnography and the multiple sleep latency test were studied. A modified Epworth Sleepiness Scale and an arbitrary cataplexy severity scale (1=minimal weakness, 2= voluntarily preventable falls, 3= falls to the ground) were utilized.

Interventions: Sodium oxybate therapy; concurrent medications were maintained.

Measurements and Results: Before sodium oxybate therapy, all subjects had suboptimally controlled sleepiness and cataplexy. Following treatment with sodium oxybate, 7/8 subjects (88%) improved. Cataplexy frequency decreased from a median of 38.5 to 4.5/ week (p=0.0078). Cataplexy severity decreased from 2.75 to 1.75 (p = 0.06). The Epworth Sleepiness Scores improved from a median of 19 to 12.5 (p= 0.02). Suicidal ideation, dissociative episodes, tremor and constipation occurred in one subject each and terminal insomnia in two. Three of the 8 (38%) discontinued therapy. Two stopped the drug owing to side effects and one due to problems with postal delivery of the medication.

Conclusions: This is the first report on sodium oxybate therapy in childhood narcolepsy-cataplexy. Our finding of improvement in cataplexy and sleepiness suggests that this medication is effective in treating severe childhood narcolepsy-cataplexy.

Keywords: Narcolepsy, cataplexy, gamma hydroxy butyrate, treatment, sodium oxybate, Xyrem

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INTRODUCTION

NARCOLEPSY IS A DISORDER OF RAPID EYE MOVEMENT (REM) SLEEP THAT IS CHARACTERIZED BY SEVERE DAYTIME SLEEPINESS, CATAPLEXY, hypnagogic hallucinations, sleep paralysis, and fragmented night sleep.[1] Approximately one third of patients have onset of symptoms prior to the age of 15 years.[2] Sleep specialists, pediatricians, and pediatric neurologists thus play a key role in its recognition and management.

There are few studies on the efficacy of psychostimulants, tricyclic antidepressants and selective serotonin reuptake inhibitors in the treatment of narcolepsy-cataplexy in childhood. Houghton et al[3] have provided a useful pharmacotherapeutic review of narcolepsy-cataplexy but have not reported on the treatment response of children with this disorder. Daytime sleepiness can be treated with moderate success in children with narcolepsy using modafinil[4] or preparations of methylphenidate and dextroamphetamines.[3] Likewise, cataplexy may respond favorably to fluoxetine and sertraline,[3] venlafaxine,[5] reboxetine,[6] viloxazine,[7] clonidine,[8] and atomoxetine.[9] The modest efficacy of these anticataplexy agents is, however, offset by adverse reactions like weight gain, anticholinergic effects, sexual side effects, and the development of tolerance. The abrupt discontinuation of tricyclic antidepressants may also precipitate status cataplecticus.[10]

Sodium oxybate (γ-hydroxybutyrate; Xyrem®) is a neurotransmitter product of γ-amino butyric acid (GABA).[11] It was approved in 2002 by the Food and Drug Administration as an orphan drug for the management of narcolepsy.[12] It is a federal schedule III controlled substance that is available only through a centralized pharmacy because of earlier diversion of the drug for recreational use. Schedule III drugs have less abuse potential than do schedule II substances and moderate dependence liability. Rigid guidelines have therefore been established for the prescription of sodium oxybate, which has to occur in conjunction with a detailed patient education program, subsequent to which the drug is shipped directly by the centralized pharmacy to the patient's home address. Sodium oxybate acts through $GABA_B$ receptors and perhaps through its own receptors.[11] It suppresses dopaminergic neuronal activity,[13,14] with a consequent increase in slow-wave sleep and a decrease in the number of nighttime awakenings, with a corresponding increase in sleep efficiency.[15,16] In adults, it reduces the frequency of cataplexy within 2 to 4 weeks of initiating therapy. The half-life is 30 to 60 minutes.[3] Adverse effects include dizziness, nausea, headache, enuresis, anxiety, leg cramps, somnambulism, sleep apnea, and early morning awakenings.[17] Treatment cessation generally does not lead to rebound cataplexy.[18]

There are no studies on the efficacy of sodium oxybate in the treatment of narcolepsy-cataplexy in childhood. We report retrospectively on the off-label use of sodium oxybate in children with severe narcolepsy-cataplexy who have been followed in our sleep disorders center. This study was performed following approval of our institutional review board and without industry funds or grants. Families purchased the medication from the centralized pharmacy.

Disclosure Statement

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Table 1—Cataplexy Severity Rating Score

Severity Score	Description of cataplexy attack
3	Patient loses posture and falls to the ground
2	Patient can maintain posture with external support, eg, holding onto a table
1	Patient has momentary weakness, eg, head drop or jaw opening but with no need to hold onto an object for support

MATERIALS AND METHODS

A diagnosis of narcolepsy was made in 8 subjects with clinical history, nocturnal polysomnography, and the Multiple Sleep Latency Test. All 8 subjects were experiencing severe cataplexy. Three of the 8 had failed treatment for cataplexy with other medications. Daytime sleepiness was also unsatisfactorily controlled in all (Epworth Sleepiness Scale [ESS] scores > 10). Histocompatibility antigen (HLA) DQB1*0602 analysis was performed in 4 of 8 of our patients as part of a separate research study but was not routinely obtained. Cerebrospinal fluid hypocretin levels were not measured because the clinical and sleep laboratory findings confirmed narcolepsy-cataplexy. The initial consultation and follow-up visits were with a certified sleep specialist (SK). Prior to initiation of treatment with sodium oxybate, each patient and family participated in an hour-long education session that was conducted by registered nurses in our sleep center. This included verbal discussion, reviewing literature, and watching a video-tape about sodium oxybate administration, followed by an opportunity to ask questions about the medication and its administration.

The frequency of cataplexy was routinely documented on each follow-up visit, based on parental and patient reports. Severity of the cataplexy was graded posthoc on an arbitrary scale (Table 1). A severity of score of 2 implied lower-extremity weakness with preservation of extensor tone of the upper extremities, whereas 3 implied trunk and upper- and lower-extremity weakness. A significant effect on cataplexy severity was defined as greater than a 50% decrease in the number of attacks, decrease in severity score of cataplexy by 1, or both the decrease in the number of attacks and in the severity score. The ESS[19] scores listed in the charts were compiled as a measure of daytime sleepiness. Because of the lack of test instruments that historically quantify sleepiness in childhood, we used a modified ESS in our subjects. An ESS question pertaining to driving required a parental estimate of the sleepiness of the child when the child was accompanying them in the automobile.

All data were gathered retrospectively from chart review and analyzed. Differences between the baseline and final ESS scores and the estimated cataplexy frequency and severity were evaluated using the Wilcoxon signed rank test.

Illustrative Case History

An 8-year-old girl (subject # 2) had subacute onset of severe daytime sleepiness. She also began to experience 4 to 5 episodes of cataplexy per day, characterized by abrupt collapse or near collapse to the floor in response to laughter, excitement, and thunderstorms. The severe sleepiness and cataplexy led to significant curtailment in social activities (refusal to attend birthday parties or laugh) and affected her academic performance. Sleep paralysis and hypnagogic hallucinations were also reported. The REM latency on nocturnal polysomnography was less than 1 minute. The Multiple Sleep Latency Test showed sleep-onset REM periods on 4 of 4 nap opportunities, with a mean initial sleep latency of 0.5 minutes. The histocompatibility antigen DQB1*0602 was present. Over the ensuing 5 years, imipramine, clomipramine, paroxetine, fluoxetine, fluvoxamine, and protriptyline were ineffective in controlling her cataplexy. Sleepiness remained uncontrolled despite therapy with methylphenidate, modafinil, amphetamine plus dextroamphetamine, methamphetamine, and dextroamphetamine in various combinations. By the age of 13 years, she had become depressed to the point of requiring admission to an inpatient psychiatric unit and had gained about 30 pounds in weight, with an increase in her body mass index from a baseline of 24 to 35 kg/m^2.

In light of the severity of the sleepiness and cataplexy, sodium oxybate was started at the age of 13 years after an extensive discussion of the potential side effects with the patient and her parents, at a dose of 1.5 gm at bed time, with repeat administration of 1.5 gm 2 hours after initial sleep onset. With gradual titration of the dose upward over an 11-month period to 3.5 gm twice nightly, cataplexy episodes decreased from 4 or 5 per day to 1 or 2 per week. Cataplexy also became less severe—she momentarily felt weakness in her legs but no longer fell to the floor. Attempts at discontinuing protriptyline were unsuccessful. She is now highly functional, participating in a full academic program at high school and in extracurricular activities such as a marching band. She no longer experiences cataplexy at birthday parties and is considering taking drivers' education classes. She was followed for a period of 28 months on sodium oxybate. She has experienced a side effect of terminal insomnia, characterized by spontaneous awakening around 5:30 AM, with a feeling of being refreshed and then being unable to fall back to sleep. Daytime sleepiness has also diminished slightly. On her last ESS assessment she had rated herself a score of 10.

Table 2—Demographics and Results of Nocturnal Polysomnograms and MSLT

			Nocturnal Polysomnography				MSLT	
Subject	Current age, y	Age at diagnosis, y	REM latency, min	AHI, no./h	PLMI, no./h	AI, no./h	Mean sleep latency, min	SOREMP, no.[a]
1	11	9	188.5	4	37.2	34.3	1.25	3/4
2	17	8	0	1	5.1	20	1	4/ 4
3	17	14	1	3	2.1	19.1	1	4/4
4	16	13	88	0	0	4.2	5.1	3/4
5	17	15	68.5	0	0.1	8.9	6	2/4
6	15	14	444[b]	3	26.3	15	1.4	1/4
7	14	13	71	3	4.4	16.2	0.1	4/4
8	15	13	162	1.2	72	4.5	3.5	5/5

[a]The number of sleep-onset rapid eye movement (REM) periods (SOREMP)/number of nap opportunities.
[b]REM latency impacted by sertraline; cataplexy confirmed independently by 2 sleep specialists.
MSLT refers to Multiple Sleep Latency Test; AHI apnea-hypopnea index; PLMI, periodic limb movement index; AI, arousal index.

RESULTS

Eight children were treated with sodium oxybate since July

Table 3—Medication History

Patient #	Age at initiation of sodium oxybate, y	Duration of . sodium oxybate therapy, mo	Drugs for sleepiness		Drugs for cataplexy	
			Prior to sodium oxybate	Maintained concomitantly with sodium oxybate	Prior to sodium oxybate	Maintained concomitantly with sodium oxybate
1	9	3	None	Modafinil	None	None
2	14	28	Methylphenidate, methamphetamine modafinil, dextroamphetamine, amphetamine/ dextroamphetamine	Modafinil, methylphenidate	Protriptyline, paroxetine, imipramine, fluoxetine, clomipramine, fluvoxamine	Protriptyline
3	15	21	Modafinil, methylphenidate, amphetamine/ dextroamphetamine	Amphetamine/ dextroamphetamine	Paroxetine, imipramine, protriptyline	Clomipramine
4	14	7	Amphetamine/dextroamphetamine, modafinil, dextroamphetamine, methylphenidate	amphetamine/ dextroamphetamine	None	None
5	16	8	Modafinil	Modafinil	None	None
6	14	10	Sertraline	dextroamphetamine, sertraline	None	None
7	13	5	Modafinil, amphetamine/ dextroamphetamine	Amphetamine/ dextroamphetamine	Amitriptyline	None
8	15	9	Modafinil	Dextroamphetamine	Fluoxetine, venlafaxine	Venlafaxine

2002. Demographics and results of nocturnal polysomnograms and MSLTs are shown in Table 2. Four of the 8 were girls. The mean age at onset of symptoms of narcolepsy was 11 years (range 8-14, SD 2) and the mean age at diagnosis was 12.38 years (range 8-15, SD 2.5, median 13 years).

Medications used to treat sleepiness and cataplexy prior to, and along with, sodium oxybate are shown in Table 3. The mean age of onset of therapy with sodium oxybate was 13.75 years (range 9-16 years, SD 2.12). The duration of therapy has ranged from 3 to 28 months, with a mean of 11.4 months (SD 8.6). The dose has ranged from 3 to 7 gm per day. The tapering of protriptyline in patient #2 led to a significant rebound increase in symptoms; consequently, we have not attempted tapering of concomitant medications in any of the other subjects.

The response to sodium oxybate is outlined in Table 4. The median number of cataplexy attacks prior to sodium oxybate treatment was 38.5 (range 3-700, SD 237), whereas, after treatment, the median fell to 4.5 (range < 1-35, SD 12.4, $p = 0.0078$). When data from the 1 outlier subject with extremely frequent cataplexy (#7) was excluded from the analysis, the difference in the cataplexy frequency before and after treatment still remained significant (median decreased from 35 to 2, $p = 0.016$). The median ESS score prior to sodium oxybate treatment was 19 (range 13-23, SD 3.4). The median posttreatment ESS score fell to 12.5 (range 9-22, SD 4.27, $p = 0.02$). The mean severity of cataplexy decreased from 2.75 (range 2-3) to 1.75 (range 1-3, $p = 0.06$).

There were side effects. Subject 1 required discontinuation of sodium oxybate because of increased nightmares and suicidal ideation. He had preexisting anxiety and an oppositional defiant disorder. Subject 4 had improvement in sleepiness and cataplexy but stopped the drug because she experienced dissociated feelings, which she described as "being out of it." Subject 5 had improvement in sleepiness and cataplexy but had to discontinue sodium oxybate because of difficulty in the timely mail delivery of sodium oxybate from the centralized pharmacy. Terminal insomnia, a known side effect in adults, occurred in 2 subjects (subjects #2 and #8); tremors (subject #3) and constipation (subject #6) were other adverse effects noted in single subjects.

DISCUSSION

This is the first case report on the efficacy of sodium oxybate in children with narcolepsy-cataplexy. Sodium oxybate appears to be effective in improving both daytime alertness and cataplexy in children with narcolepsy. The dramatic difference in pretreatment and posttreatment cataplexy frequency is confounded by the fact that 1 patient (subject #7) had more than 100 attacks a day prior to sodium oxybate. Even if data from this patient are excluded, however, the effects of sodium oxybate on cataplexy frequency remained significant. We acknowledge the difficulty in accurately quantifying the cataplexy episodes and had to depend on retrospective parental and patient reports.

Periodic limb movements can contribute to fragmented night sleep in narcolepsy. The improved daytime alertness in our patients may be due to either the suppression of the periodic limb movements (subject #1, #6, and #8) or improved sleep architecture via other mechanisms that still need to be identified. The favorable response to sodium oxybate may in part be attributable to the fact that parents ensured compliance with ingestion of the drug at bedtime, and they usually administered both doses of sodium oxybate. This was true of all our patients except subject #4, whose parent also suffered from sleepiness resulting from narcolepsy.

The occurrence of suicidal ideation has been reported in a case of sodium oxybate abuse.[20] Its occurrence in 1 of our 8 subjects was confounded by the fact that this patient also had a known anxiety disorder and oppositional disorder. A history of preexisting psychiatric symptoms may therefore be a contraindication

Table 4—Results of Treatment with Sodium Oxybate

Subject #	Cataplexy severity		Cataplexy attacks, no./wk		Epworth Sleepiness Scale score		Treatment duration with sodium oxybate, mos.	Adverse effects of treatment	Improvement in social spheres
	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy			
1	3	1	4	2	23	17	3	Suicidal gesture	No
2	3	1	35	7	20	10	28	Terminal insomnia	Yes
3	2	1	105	< 1	18	11	21	Tremor	Yes
4	3	2	42	9	13	9	9	Nausea, dissociative feeling	Don't know
5	2	2	10	< 1	21	22	8	Problem in mail delivery of medication	Yes
6	3	3	56	21	22	13	10	Constipation	Yes
7	3	3	> 700	35	16	15	5	None	Yes
8	3	1	3	1	17	12	9	Terminal insomnia	Don't know

to the use of sodium oxybate. Terminal insomnia, a recognized side effect, occurred in 25% of our patients but did not appear to be disabling. Tremors were similar to that observed in adults. In contrast with findings from adults, however, we did not observe obstructive sleep apnea, enuresis, sleep walking, bed wetting, or headache. Because of the small sample size, it is not possible to draw additional inferences.

A physician should prescribe sodium oxybate only when the potential for abuse has been deemed unlikely, based upon close interaction with the family. Before starting sodium oxybate, we routinely spend 1 to 2 hours on patient and family education. We were reassured to observe that subject #4 actually stopped sodium oxybate on her own when she experienced a psychosensory disturbance.

There seemed to be impressive strides made in the social spheres with almost all of our patients who continued sodium oxybate. It may be of interest to follow this cohort for a longer period of time.

The limitations of this study are that it was retrospective and that there were only 8 subjects studied, of whom 3 discontinued the drug for various reasons, as described previously. Only 3 subjects continued the medication for 10 or more months. Further, the concurrently administered medications may have also contributed to clinical improvement.

Rational pharmacotherapy of childhood narcolepsy implies targeting the symptom that is most bothersome to the patient. If daytime sleepiness is severe and cataplexy is less prominent, the initial prescription of modafinil or preparations of methylphenidate and amphetamine seems appropriate, with sodium oxybate as follow up if daytime sleepiness and fragmented sleep persist. When cataplexy is the more disabling symptom, however, consideration should be given to initiating treatment with sodium oxybate at the onset, provided that there are no medical, social, and family contraindications. Our experience and the recent findings in adults suggest that sodium oxybate can improve both cataplexy as well as daytime sleepiness[21] in narcolepsy.

A randomized, double-blind, placebo-controlled, multicenter trial is indicated to further assess the efficacy of sodium oxybate in children. Further interest in this medication is likely, as has been suggested by a recent review on emerging therapies for narcolepsy-cataplexy.[22]

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