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Original Article

Sodium oxybate in the treatment of childhood narcolepsy–cataplexy: A retrospective study

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ABSTRACT

Objective: To evaluate the efficacy and side effect profile of sodium oxybate in the treatment for narcolepsy–cataplexy in the pediatric age group.

Methods: A retrospective study was conducted on 15 children and adolescents with narcolepsy–cataplexy who had been treated with sodium oxybate. The mean age at diagnosis of narcolepsy was 11 years (range 3–17 years). Subjects were followed for 3–90 months (mean 33) after starting sodium oxybate. During this period of time they were also maintained on other medications for sleepiness ($n = 14$) and cataplexy ($n = 6$). The charts were reviewed for documentation of improvement in sleepiness or cataplexy, side effects, and functioning in daily life.

Results: Subsequent to the addition of sodium oxybate, sleepiness improved in 13/15 patients. In patients who had Epworth Sleepiness Scale (ESS) assessments, the score fell from a baseline median of 18 to 12 ($n = 10$, $p = 0.01$). The number of cataplexy episodes estimated by parents decreased from a median of 38/week pre-treatment to <1/week post treatment ($n = 14$, $p < 0.001$). Cataplexy severity, measured on an arbitrary scale, fell from a median of 3 (severe) to 1 (mild) in all 15 subjects ($p < 0.001$).

Two of the 15 patients (13%) discontinued sodium oxybate, one for insurance reasons and the other due to constipation and dissociative feelings. A third patient stopped the medication temporarily due to body aches and dizziness, but then resumed treatment without recurrence of symptoms. Side effects in four others included tremor, blurring of vision, nocturnal awakenings, and increased nightmares. Overall, side effects occurred in 6/15 (40%) individuals. Improvement in social/academic spheres was noted in 11/15 (73%) subjects after starting sodium oxybate. The median BMI before and after treatment remained unchanged at 23 ($n = 14$, $p = 0.99$). Median values of height and weight before and after treatment also did not change significantly. The mean dose of sodium oxybate was 5 ± 2 g. Dose escalation owing to development of tolerance was not encountered.

Conclusions: Sodium oxybate is effective in alleviating sleepiness and cataplexy in childhood onset narcolepsy–cataplexy. The therapeutic response was sustained over time, and without development of tolerance. Forty percent of the subjects experienced adverse effects.

1. Introduction

Sodium oxybate (gamma hydroxybutyrate; Xyrem®) was approved in 2002 by the Food and Drug Administration (FDA) for treating sleepiness and cataplexy in adults with narcolepsy [1]. Owing to its abuse potential, the medication has been conventionally prescribed after intensive patient education and dispensed through a central pharmacy. The mechanism of action of the drug has not been fully elucidated, but it is felt to act on GABA-B receptors [2]. Due to the short elimination half-life of 0.5–1 h, it is usually administered in two divided doses, the first immediately prior to bedtime and the second two and a half hours later [3].

In a randomized, controlled clinical trial in adults the drug has reduced the frequency of cataplexy [1]. It increases stage N3 sleep and sleep efficiency, with a commensurate improvement in daytime sleepiness [4]. The drug is generally used in conjunction with other medications for sleepiness [5]. Unlike other agents, a rebound increase in cataplexy upon its discontinuation or tolerance to its effects is infrequent [6]. Common side effects include nausea, abdominal discomfort, constipation, dizziness, headache, tremor, enuresis, NREM parasomnias, early morning awakenings, and respiratory depression [6].

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Sodium oxybate has been used on off label basis for treating narcolepsy–cataplexy in children, but there is limited information regarding its long term efficacy and safety in this population [7,8]. A retrospective study from our center had in 2006 reported on the efficacy and side effects of sodium oxybate in treating childhood narcolepsy–cataplexy [8]. The present study expands upon our experience with sodium oxybate using a larger number of subjects who have been followed over a longer period of time (up to 90 months). This was a retrospective chart review. This study was approved by the Institutional Review Board (IRB). Prior to commencing therapy, the patients and their families received education about sodium oxybate using the help of our sleep center nursing staff. The medication was dispensed to the patients and their families using a centralized pharmacy and the Xyrem Success Program®.

2. Methods

Subjects under the age of 18 years who had been diagnosed with narcolepsy–cataplexy at our institution based upon clinical history, nocturnal polysomnography (PSG), and the multiple sleep latency test (MSLT) were included. The patients had presented with excessive daytime sleepiness; 13 of 15 had cataplexy at disease onset. Two subjects developed cataplexy a few months following presentation. Data on age at the start of the present study, age at the time of diagnosis, gender, ethnicity, and baseline PSG and MSLT findings were collected. Results of Human Leukocyte Antigen (HLA) for the DQB1*0602 haplotype and cerebrospinal fluid hypocretin level, when obtained, were documented. The following information was also gathered: sodium oxybate start and stop dates, its initial and maintenance dose, side effects, reason(s) for discontinuation, other medications for sleepiness and cataplexy that had been used prior to treatment with sodium oxybate, and medications that were maintained concurrently.

Epworth Sleepiness Scale (ESS) scores at the time of initiation of sodium oxybate treatment and at the last follow up visit were recorded. Parental and patient estimates were gathered on the number of cataplexy episodes per week prior to the commencement of sodium oxybate therapy and also at the time of the last follow up visit. Cataplexy severity was graded using an arbitrary scale previously described in our earlier report – grade 3 is complete loss of posture with fall to the ground; grade 2 is weakness with upright posture being maintained using an external support, such as holding onto a table; grade 1 is momentary weakness without the need to hold onto an object for support, such as head drop or the jaw falling open.

Improvement in social and academic spheres, if documented at follow up visits, was noted. Information on body mass index (BMI), height, and weight at baseline and at last follow up visit was recorded from the clinic visits. Information on co-morbidities, including coexisting sleep disorders was collected.

Statistical analysis was performed using JMP(R) software. The independent *t*-test was used to compare sleepiness scores, BMI, and frequency and severity of cataplexy before and after treatment with sodium oxybate. The Wilcoxon sign-rank test for non-parametric data was used to account for any outliers that may have skewed the results, such as a high frequency of cataplexy episodes of 100 per day in one patient.

3. Results

Fifteen narcolepsy–cataplexy subjects who were below the age of 18 years at diagnosis were treated with sodium oxybate – 53% were male; 73% were Caucasian. The mean age at the time of diagnosis was 11 years (range 3–17 years, SD 4.3). In Table 1, patient #1–8 are from our previous study [8], included because of extension of the period of their follow up.

Nocturnal polysomnography showed a mean initial sleep latency of 7 min (range 0–60, SD 15) and a mean REM latency of 91 min (range 0–228, SD 63). The mean values for the apnea–hypopnea index, periodic limb movement index, and arousal index were 1.3 (range 0–3, SD 1.2), 15 (0–37, SD 13), and 16 (range 4–34, SD 7), respectively. In a minority of patients, the numerical values for apnea–hypopnea index (subjects #1, 7), the periodic limb movement index (subjects #1, 8), and the arousal index (subjects #1, 8) were not available, but were described as "not significant" for each of these indices in the electronic medical record.

The mean initial sleep latency on MSLT in the 14 subjects in whom testing was performed was 2.3 min (SD 2) and the mean number of SOREMs were three (SD 1). The fifteenth patient (subject #14) was three years old at presentation and thus did not qualify for MSLT. Histocompatibility antigen DQB1*0602 testing was performed in five of 15 (33%) subjects, and was positive in 4/5 subjects. CSF hypocretin levels were checked in two (13%) patients, one of whom presented with sleepiness and severe cataplexy at the age of three years (subject #14, level 26.8 pg/ml; reference value >110 pg/ml). In the second patient (subject #15), the CSF hypocretin level was 0 pg/ml.

The mean age at the time of initiation of sodium oxybate was 12 years (range 4–17 years, SD 4). The mean initial starting dose was 3 g (range 1.5–4.5, SD 0.7), and the mean maintenance dose was 5 g (range 3–9, SD 2). The average duration of therapy was

Table 1
Patient demographics and sodium oxybate treatment details.

No.	Age at diagnosis of narcolepsy (years)	Gender M = male F = female	Age at initiation of sodium oxybate (years)	Current age (years)	Initial dose (g)	Maintenance dose (g)	Duration of treatment (months)
1	8	F	14	22	3	9	63
2	13	F	14	22	3	4	16
3	14	M	14	22	3	8	85
4	9	M	10	16	1.5	4	89
5	16	F	16	23	3	3	57
6	14	M	14	21	3	6	26
7	13	M	13	19	4	6	3
8	14	F	15	21	4.5	7.5	58
9	4	M	5	13	3	5	24
10	11	F	11	16	3	5	35
11	17	M	17	19	3	6	11
12	13	F	13	14	3	4	7
13	9	M	15	16	3	3	11
14	3	F	4	4	2	2	5
15	6	M	7	7	3	3	6