Long-term follow-up on the effects of sodium oxybate on daytime sleepiness and sleep architecture in patients with narcolepsy type 1

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Introduction. Sodium oxybate (SXB) was administered for the first time in 1979 in 16 patients with narcolepsy with cataplexy (NT1) that improved up to 20 months.

Aims. To evaluate the effect of SXB on daytime sleepiness and sleep architecture by video-polysomnography in a sample of 23 NT1 adult patients (13 men, 10 females) treated up to three years. Additional goal was to study the presence of sleep comorbidities.

Patients and methods. NT1 patients were diagnosed according to International Classification of Sleep Disorders, third edition. We conducted a longitudinal observational study and a video-polysomnography comparing the sleep parameters of patients treated with an initial nocturnal dose of 4.5 g of SXB after six months (FU-1), one year (FU-2) and three years (FU-3) of uninterrupted treatment. Video-polysomnography parameters were analyzed including apnea-hypopnea and periodic leg movements indexes.

Results. Patients were HLA-DQB1*06:02 positive except a familial case. Thirteen patients (56%) discontinued SXB treatment over the three-year of the study. The two-nightly doses has been one of the reason for discontinuing treatment as well as insufficient compliance, mild or severe side effects, comorbidities and pregnancy. We found significant differences at FU-2 in sleep structure with an increased in stage N2 ($p < 0.03$) and a higher periodic leg movements index ($p < 0.01$). At FU-3 we found significant differences in sleep structure with an increase in stage N1 ($p = 0.03$) and in comorbidities (periodic leg movements and apnea-hypopnea indexes). There was not significant change on daytime sleepiness during the study.

Conclusions. SXB was administered in low-medium doses. Two-nightly doses and sleep fragmentation linked to sleep comorbidities at long-term lead to drug withdrawal.

Key words. Narcolepsy with cataplexy. Nocturnal disturbed sleep. Sleep fragmentation. Side effects. Sodium oxybate. Video-polysomnography.

Introduction

Gamma-hydroxybutyrate, in its sodium form –sodium oxybate (SXB)– an endogenous metabolite of gamma-aminobutyric acid, is a central nervous system depressant, that was administered for the first time in 1979 in 16 narcolepsy with cataplexy (NT1) patients that improved without development of tolerance up to 20 months [1]. The availability of SXB as treatment for NT1 patients has significantly enlarged the therapeutic options and in addition has improved the quality of life of many patients [2].

Disturbed nocturnal sleep is significant in 65% of NT1patients and is characterized by sleep fragmentation due to stage shifts with a great impact in the nocturnal sleep quality and, as a consequence, excessive daytime somnolence [3].

The aims of this study were as follows: a) to evaluate with video-polysomnography the effect of SXB focusing on sleep architecture in our sample of 23 adults NT1 patients treated uninterruptedly up to three years. Moreover, the additional goal was b) to study the presence of sleep comorbidities in the sample, obstructive sleep apnea, periodic limb movements during sleep, and REM sleep behavior disorder.

Patients and methods

A sample of 23 NT1 consecutive caucasian patients (13 males, 10 females) with a mean age of 42.2 ± 13.7 years, were recruited from our outpatient Sleep Unit, Clinical Neurophysiology Service

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of the Hospital General Universitario Gregorio Marañón (Universidad Complutense de Madrid). NT1 patients were diagnosed using the International Classification of Sleep Disorders, third edition [4].

In addition, a full medical history and anthropometric measurements were performed. The patients reported excessive daytime sleepiness and cataplectic attacks, disturbed nocturnal sleep and other accessory symptoms (sleep paralysis and/or hypnagogic hallucinations) which were assessed based on medical history, sleep diaries and questionnaires. Epworth sleepiness scale was used to determine excessive daytime sleepiness. HLA-typing showed DQB1*06:02 positivity in all patients except in one familial case [5].

In this longitudinal observational study the initial dose of SXB oral solution, dispensed by the hospital pharmacy was 4.5 g given as two equally divided doses with an interval of 2.5-3 hours, followed by escalating doses at subsequent three-week intervals to the final dose (range, 4.5-9 g). Patients were recommended to abstain from alcohol and hypnotics due to possible respiratory depression.

Routinely all NT1 patients were followed in the outpatient clinic every six month. A standard video-polysomnography was performed six months after the SXB treatment was initiated (follow-up, FU-1); repeated one year later (FU-2), and at three years (FU-3) of uninterrupted SXB. Excessive daytime sleepiness, drug compliance and side effects were evaluated during follow-up visits. The video-polysomnography parameters analyzed were: sleep efficiency index; sleep latency; REM latency; wakefulness after sleep onset; stages N1, N2, N3 and REM; total number of awakenings/hour (from any sleep stages to wakefulness); apnea-hypopnea and periodic leg movements indexes.

Recordings were manually scored according to the American Academy of Sleep Medicine, *Manual for the scoring of sleep and associated events*, version 2.6. [6]. Visual quantitative analysis for REM without atonia was performed. The background activity varied from 0.5 to 2 μV in all subjects. Tonic, phasic and any (either tonic or phasic) percent muscle activity was visually determined, manually scored, and analyzed using 30-second epochs in the submental and tibialis anterior muscles [7]. The same specialist (R.P.A.) supervised all the video-polysomnography.

The local Clinical and Research Ethics Committee approved the study, which was conducted according to the Declaration of Helsinki. The patients signed an informed consent form.

Statistical analyses

Quantitative variables are expressed as mean and standard deviation or median an interquartile range. Qualitative variables are expressed as frequency. Each follow-up parameters were compared to each other using Wilcoxon signed-rank test. Differences were statistically significant if $p < 0.05$. The analyses were performed using SPSS Statistics for Windows, version 23.0.

Results

Demographic characteristics

NT1 patients were 13 males and 10 females with a mean age at FU-1 of 42.2 ± 13.7 years. No significant differences in body mass index between the first and the subsequent follow-ups were found.

Clinical symptoms

A reduction of cataplexy and hypnagogic hallucinations was observed in all patients throughout the study. There was not significant change of excessive daytime sleepiness according to Epworth sleepiness scale during the three-years treatment period when administered SXB alone or in combination with a single dose of modafinil 200 mg in the morning.

Side effects

Thirteen patients (56, 5%) discontinued SXB treatment. The reasons for withdrawal were pregnancy (n = 1) and insufficient compliance (most patients complaint about the two-nightly doses). Mild side effects were dizziness, enuresis, unpleasant feeling of coldness after the first dose (reported by three females), and unintentional weight loss in female non-obese patients common in the first months of treatment (n = 9). Comorbidities and severe side effects were, one unspecified psychosis that occurred after the initiation of SXB in a patient treated with 200 mg of modafinil, hypertension and depression (n = 3).

Sleep fragmentation in the last third part of the night –showed by video-polysomnography– was very unpleasant in all patients from FU-1 onwards. This finding was consistent in all patients and independent of the second dose administered and the interval after the first dose.

Video-polysomnography parameters

The video-polysomnography parameters analyzed are summarized in table I. We observe after the administration of the first dose, an increase in stage N3 in the first sleep cycle and a REM-onset in 90% of patients. When comparing the time spent in the different sleep stages between FU-1 and FU-2, patients increased the time spent in stage N2 (z = –2,17; p = 0.03). At FU-3, we found a significant increase in the time spent in stage N1 (z = –2,09; p = 0.03). At the latest follow-up (FU-3), the time spent in stages N1 and N2 were significantly longer than at FU-1 (z = -2.36; p = 0.01).

Table I summarizes the polysomnography parametric analyses at each follow-up, and figure represents the median time in sleep stages during subsequent follow-ups.

Sleep disorders comorbidities

Two patients developed REM sleep behavior disorder while on 4.5 g/day of SXB and in another patient appeared *de novo* at the same dose. Apnea-hypopnea index increases significantly in obese patients without variation in the body mass index. The apnea-hypopnea index was significant higher at FU-3 (z = –2.66; p = 0) (Table II).

SXB was associated significantly with an increase in periodic leg movements index and it was significantly higher at FU-2 (z = –2.52; p = 0.01) and at FU-3 (z = –2.02; p = 0.04) compared to FU-1.

No one patient who discontinued SXB had rebound cataplexy.

Discussion

To our knowledge, the treatment with SXB in the sample is the longest in the literature to evaluate the effect on sleep architecture and comorbidity with video-polysomnography.

In a retrospective study of 90 NT1 patients 55.6% of them experienced an adverse effect, the drug had to be discontinued with subsequent resolution of the side effects with older patients being more vulnerable [8]. In our sample even if the same specialists carried out the follow-up –which increases adherence to treatment–, the percentage of side effects was 56.5%, the doses administered were lower and the patients were younger. In addition, the most common complain was the two-nightly doses.

Retrospective classical studies showed that the first administration of SXB in NT1 patients was fol-

Table I. Demographic and anthropometric characteristics, Epworth sleepiness scale, polysomnography parameters and SXB dose during follow-ups.

	Follow-up1 n = 23 Mean (SD)	Follow-up2 n = 16 Mean (SD)	Follow-up3 n = 10 Mean (SD)	p value FU-1 versus FU-2	p value FU-1 versus FU-3
Age (years)	42.2 (13.75)	42.38 (13.95)	44.2 (16.01)	NS	NS
Sex (m/f)	13/10	8/8	5/5	–	–
BMI kg/m^2	28.61 (5.19)	27.21 (5.9)	26.4 (6.01)	NS	NS
SXB dose (g)	4.5 (1.15)	5.25 (1.62)	5.47 (0.86)	NS	NS
Epworth	17.67 (7.5)	18 (7)	20.5 (4.9)	NS	NS
Sleep efficiency (%)	78.57 (13.17)	78.99 (8.64)	78.92 (8.68)	NS	NS
Sleep latency (min)	8.02 (5.68)	8.65 (7.95)	6.5 (3.35)	NS	NS
REM sleep latency (min)	33.17 (48.01)	33.31 (48.01)	35.06 (50.34)	NS	NS
TST (min)	382.63 (55.16)	377.96 (52.25)	384.9 (46.52)	NS	NS
WASO (min)	90.75 (59.81)	95.37 (41.52)	102.25 (40.4)	NS	NS
Awakenings/hour (n.º/h)	17.68 (12.11)	15.93 (10.74)	12.3 (4.39)	NS	NS
Stage N1 (minutos)	68.26 (28.39)	78.12 (54.97)	104.5 (80.49)	NS	0.03[a]
Stage N1 (%)	17.61 (7.09)	17.39 (10.24)	21.37 (16.48)		
Stage N2 (minutos)	136.674 (52.01)	150.37 (48.41)	148.45 (52.72)	0.03[a]	NS
Stage N2 (%)	33.84 (9.5)	35.01 (10.89)	30.32 (10.5)		
Stage N3 (minutos)	102.02 (54.64)	87.78 (48.1)	89.65 (55.59)	NS	NS
Stage N3 (%)	26.39 (13.74)	21.11 (12.61)	18.48 (11.7)		
Stage REM (minutos)	50.95 (16.65)	50.87 (20.04)	42.35 (19.77)	NS	NS
Stage REM (%)	13.09 (4.58)	11.68 (4.09)	8.66 (3.93)		
AHI (Median, IQR)	2.65 (0-9.6)	2.8 (0-6.6)	4.05 (3.1-19)	NS	0[a]
PLMI (Median, IQR)	0 (0-7.3)	17.65 (3.6-27.22)	19.35 (15.2-31.4)	0.01[a]	0.04[a]

AHI: apnea-hypopnea index; BMI: body mass index; IQR: interquartile range; NS: not significant; PLMI: periodic leg movement index; PSG: polysomnography; REM: rapid eye movements; SXB: sodium oxybate; TST: total sleep time; WASO: wake after sleep onset. [a]Significant differences at $p < 0.05$.

Figure. Histograms of distribution of total sleep time and sleep stages (in minutes) during consecutive follow-up visits. *Significant differences at $p < 0.05$. REM: rapid eye movements; TST: total sleep time.

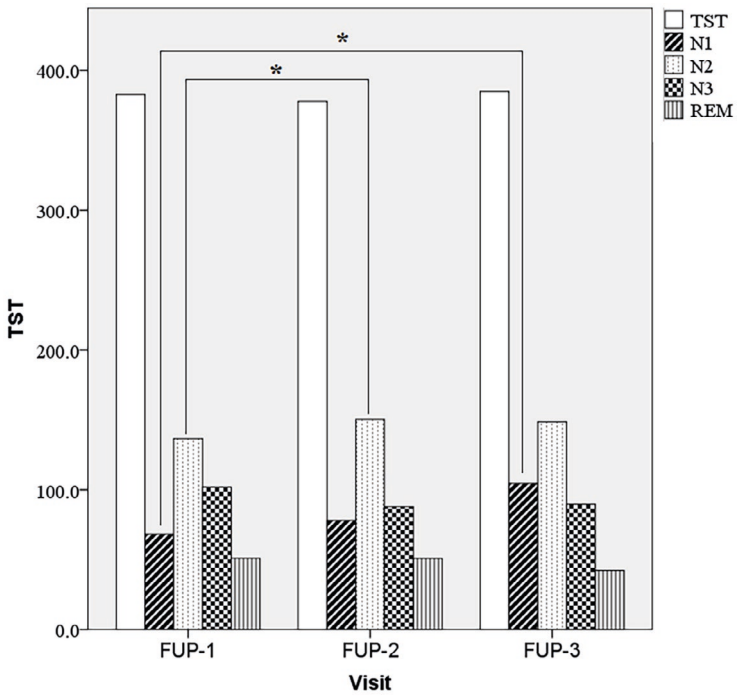

Table II. BMI is the mean value of the whole group during successive follow-ups. No significant changes in BMI were found through the study. BMI ≥ 30 kg/m^2 = obesity.

Visit	BMI > 30 kg/m^2	AHI (mean)
FUP-1	6/23 (26%) (range 30-39)	5.61
FUP-2	4/16 (25%) (range 30-38.9)	4.29
FUP-3	2/10 (20%) (range 30-36.8)	2 patients (AHI >30)

AHI: apnea-hypopnea index; BMI: body mass index.

lowed by an immediate important effect on video-polysomnography including an increase in high voltage slow wave sleep (stage N3) [9]. We observe after the administration of the first dose in all video-polysomnography and in successive follow-ups, an increase in stage N3 in the first sleep cycle, a REM-onset in 90% of the patients without significant differences in sleep latency and total sleep time. The effects of SXB on sleep architecture were examined in a study on 25 NT1 patients in whom the maintenance of wakefulness test and Epworth sleepiness scale were used to determine the effects on excessive daytime sleepiness [10]. Patients were maintained on their usual daytime stimulant dose and they received 4.5 g of SXB for four weeks followed by escalating doses. SXB at bedtime reduced the already short REM sleep latency and increased the duration of REM sleep in four hours that followed. After four weeks, this effect on REM sleep disappeared and escalating doses of SXB then depressed the duration of REM sleep and increased that of slow wave sleep. Total sleep time was not increased same as in our study, even though the number of nocturnal awakenings declined significantly that did not happen in our long-term study.

In a study by Roth et al [11], evaluable polysomnography data from 159 NT1 patients, including shifts from stage N1 to wake, were from a randomized, placebo-controlled trial of SXB. Treatment lasted eight weeks with placebo or SXB 4.5, 6 or 9 g. Improvements from baseline in reported sleep quality were significantly greater with SXB 4.5 and 9 g at week eight. This studio concludes that SXB showed improvements in sleep continuity and nocturnal sleep quality that are characteristic of disturbed nocturnal sleep but SXB treatment lasted only two months.

In our sample, the number of awakenings per hour of sleep (from any sleep stage) decreased progressively but not significantly over the time probably because the dose administered was lower in order to avoid side effects. Sleep fragmentation with stage shifts appeared to be higher in the last third part of the night.

Seeck-Hirschner et al [12] reported two patients with narcolepsy with cataplexy and obstructive sleep apnea treated with SXB in whom there was an increase in sleep-related breathing disturbances. In our sample, none patients had obstructive sleep apnea at FU-1 and FU-2 even though six out of 23 and four out of 16 respectively were obese (body mass index = 30 kg/m^2). Two male patients out of 10 (20%) developed obstructive sleep apnea (>30) at FU-3. These patients were treated with continuous positive airway pressure. The apnea-hypopnea index increases at FU3 after adjusting for body mass index. No significant changes in body mass index were found through the study. Some changes between FU-1 and the last FU-3 may be due in part to the dropouts (23 at FU-1 versus 10 patients at FU-3).

Bédard et al found that SXB in narcolepsy with cataplexy was associated with an increase in periodic leg movements that have the potential of op-

posing the sleep consolidation effect of the substance. They discuss these results in relation to the role of dopamine in the physiopathology of narcolepsy and periodic leg movement [13]. We observed in our sample a significant increase of periodic leg movements at FU-2 and FU-3 that may be due in part to the aging and the disease progression and not only to the SXB treatment. In general, patients did not report more restless legs syndrome.

There are two patients in the literature in whom the SXB has been efficacious in the control of REM sleep behavior disorder symptoms at low doses [14,15]. In a single observational study of a NT1 patient with a comorbid, severe REM sleep behavior disorder the efficacy of SXB was dose-dependent [16]. In a Spanish NT1 family, two members developed REM sleep behavior disorder while on SXB treatment at low doses (4.5 g) [5]. Moreover, REM sleep behavior disorder was unchanged in one case *de novo* independently of the dose administered. We occasionally found isolated episodes of somnambulism at the start of treatment as well as enuresis mentioned as an adverse effect of treatment.

A reduction of cataplexy and hypnagogic hallucinations clinically assessed was observed in all patients through the study [17]. No one patient who discontinued SXB had rebound cataplexy [18].

One limitation of the study is the small number of patients who continued treatment up to three years period due to drug dropouts because of insufficient compliance, side effects, comorbidities and lack of effectiveness in control of excessive daytime sleepiness and disturbed nocturnal sleep.

Another limitation of the study is that some changes observed between the interval of diagnosis and successive follow-ups with SXB treatment may be due to the aging and the disease progression.

Conclusion

SXB was administered in adults NT1 patients at low-medium doses up to three years. Lack of effectiveness in control of excessive daytime sleepiness and sleep fragmentation with a great impact in sleep continuity and quality together with the presence of comorbidities at long-term administration led to drug withdrawal.

Future prospective studies have to look at disturbed nocturnal sleep in dependence of the SXB dose. A longer half-life with a better pharmacokinetic profile would also make SXB more acceptable for the treatment of NT1 patients.

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Efecto a largo plazo del oxibato de sodio en la somnolencia diurna y en la estructura del sueño en pacientes con narcolepsia de tipo 1

Introducción. El oxibato de sodio (SXB) se utilizó en 1979 en 16 enfermos con narcolepsia-cataplejía (NT1) que mejoraron tras 20 meses de tratamiento.

Objetivos. Evaluar el efecto del SXB en la somnolencia diurna y en la estructura del sueño mediante videopolisomnografía en una muestra de 23 enfermos de NT1 (13 hombres y 10 mujeres) tratados durante tres años. Investigamos adicionalmente la presencia de comorbilidad.

Pacientes y métodos. Diagnosticamos a los enfermos de acuerdo con la Clasificación Internacional de Trastornos del Sueño, tercera edición. Realizamos un estudio longitudinal, observacional y de videopolisomnografía, comparando los parámetros de sueño y los índices de apnea-hipopnea y de movimientos periódicos de las piernas de los enfermos, tratados con una dosis nocturna inicial de 4,5 g de SXB al cabo de seis meses (C-1), un año (C-2) y tres años (C-3) de tratamiento ininterrumpido.

Resultados. Todos los enfermos eran HLA-DQB1*06:02 positivos, excepto un caso familiar. Trece enfermos (56%) interrumpieron el tratamiento debido a las dos tomas nocturnas, así como a la presencia de efectos secundarios, comorbilidad y embarazo. Encontramos diferencias significativas en C-2 en la estructura del sueño con aumento del estadio N2 ($p < 0,03$) y del índice de movimientos periódicos de las piernas ($p < 0,01$). En el control C-3 encontramos diferencias significativas en la estructura del sueño con aumento del estadio N1 ($p = 0,03$), y de los índices de movimientos periódicos de las piernas y de apnea-hipopnea.

Conclusiones. El SXB se administró en dos dosis nocturnas, lo que, unido a la fragmentación del sueño y a la aparición de comorbilidades, condujo a la interrupción del tratamiento a largo plazo.

Palabras clave. Efectos adversos. Fragmentación del sueño. Narcolepsia con cataplejía. Oxibato de sodio. Sueño nocturno perturbado. Videopolisomnografía.