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Original Article

An observational clinical and video-polysomnographic study of the effects of clonazepam in REM sleep behavior disorder

Raffaele Ferri [a,*], Sara Marelli [b], Luigi Ferini-Strambi [b], Alessandro Oldani [b], Francesca Colli [b], Carlos H. Schenck [c], Marco Zucconi [b]

[a] Department of Neurology I.C., Oasi Institute for Research on Mental Retardation and Brain Aging, IRCCS, Troina, Italy
[b] Sleep Disorders Centre, Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Vita-Salute University, Institute and Ospedale San Raffaele, Milan, Italy
[c] Minnesota Regional Sleep Disorders Centre, Department of Psychiatry, Hennepin County Medical Center, University of Minnesota Medical School, Minneapolis, MN, USA

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ABSTRACT

Objective: To analyze the differences in sleep structure and nocturnal motor activity between drug-free REM sleep behavior disorder (RBD) patients and those under therapy with clonazepam, and to evaluate the long-term longitudinal changes under continued therapy with clonazepam.
Methods: Fifty-seven consecutive iRBD patients were recruited (52 men and 5 women, mean age 68.8 ± 6.03 years). Forty-two patients were not taking any medication at the time of the evaluation (iRBD − Clo) while 15 were taking clonazepam (0.5–1 mg) at bedtime (iRBD + Clo). The Clinical Global Impression-Severity (CGI-S) scale was obtained. Sleep was video-polysomnographically recorded and the RBD severity scale (RBDSS) obtained. The chin EMG amplitude was quantitatively assessed and the Atonia Index computed.
Results: Disease duration was significantly longer in iRBD + Clo patients who also showed a lower rate of stage shifts, higher sleep efficiency and lower percentage of wakefulness after sleep onset and of sleep stage 1, and an increased percentage of sleep stage 2. The longitudinal long-term follow up study in a subgroup of 13 patients showed moderately increased total sleep time, sleep efficiency, sleep stage 2, slow-wave sleep and decreased wakefulness after sleep onset and sleep stage 1, under clonazepam treatment. The CGI scale clearly tended to improve after treatment, but no common trend was evident for RBDSS or Atonia Index.
Conclusions: This study provides evidence of important objective effects of clonazepam on NREM sleep in RBD; this data might be very important for the development of new and effective treatments for this condition.

1. Introduction

Bedtime clonazepam is universally accepted to be a first-line treatment for REM sleep behavior disorder (RBD). Although for sleep disorders, clonazepam was initially used as therapy of what was previously called "nocturnal myoclonus" (later identified as periodic leg movements during sleep); it was subsequently found to be very effective in controlling RBD. Moreover, clonazepam was found to control not only the abnormal behaviors of RBD, but also the associated disturbed dreaming, another hallmark of RBD.

Notwithstanding several large case series that have reported a response rate to clonazepam therapy of close to 90% [1] and its relative safety, without apparent dosage tolerance despite years of nightly therapy [2], there are no double-blind, placebo-controlled, randomized trials of therapy of RBD with clonazepam [3,4]. Moreover, it is difficult to devise such a study in an ethically feasible manner, given the risk of recurrent injuries usually associated with RBD (with major morbidity and potential lethality).

Although little is known on the mechanism of action of clonazepam in RBD, in a single small study it appeared to suppress the excessive phasic motor-behavioral activity [5], rather than restore REM-atonia. Clonazepam also appears to strongly modify the abnormal dream content that usually emerges with the abnormal behaviors of RBD [2].

Studies analyzing in detail the modifications induced by clonazepam on sleep structure and motor activity during sleep are also scarce. Further information on this topic might prove to be important for understanding the mechanism of action of clonazepam and

* Corresponding author. Address: Sleep Research Centre, Department of Neurology I.C., Oasi Institute for Research on Mental Retardation and Brain Aging, IRCCS, Via C. Ruggero 73, 94018 Troina, Italy. Tel.: +39 0935 936111; fax: +39 0935 936694.
E-mail address: rferri@oasi.en.it (R. Ferri).

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possibly also for formulating new therapeutic strategies. For this reason, the aim of this study was to analyze the differences in sleep structure and nocturnal motor activity between drug-free RBD patients and those under current therapy with clonazepam. Additionally, the long-term longitudinal changes under continued therapy with clonazepam were evaluated in a subgroup of patients.

2. Subjects and methods

2.1. Subjects

Patients with idiopathic RBD (iRBD) attending the Sleep Disorders Center of the San Raffaele hospital of Milan were consecutively and retrospectively recruited for this study. The diagnosis of iRBD was based on the International Classification of Sleep Disorders, 2nd Edition (ICSD-2) criteria [6] for RBD, including presence of REM sleep without atonia, sleep related injurious, disruptive behaviors by history or abnormal sleep behaviors documented during polysomnographic monitoring, absence of EEG epileptiform activity during REM sleep, sleep disturbance not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder. Secondary forms of RBD were excluded on the basis of historical data, neurologic examination, and encephalic MRI findings. All RBD patients with at least one subtentorial vascular lesion or at least two vascular supratentorial lesions greater than 0.5 cm were excluded.

A careful history was collected for all patients in order to evaluate the age at onset of their symptomatology and also the Clinical Global Impression-Severity scale was obtained. In particular, patients that were never treated before with clonazepam were identified, as well as those under current treatment with this medication.

This study was approved by the local ethics committee and all subjects provided informed consent according to the Declaration of Helsinki.

2.2. Nocturnal polysomnography

Nocturnal video-polysomnography (videoPSG) was carried out in a standard sound-attenuated (noise level to a maximum of 30 dB nHL) sleep laboratory room. Subjects were not allowed caffeinated beverages the afternoon preceding the recording and were allowed to sleep-in until their spontaneous awakening in the morning. Lights-out time was based on individual habitual bed time and ranged between 21.30 and 23.30 h. The following signals were recorded: EEG (at least two channels, one central and one occipital, referred to the contralateral earlobe); electrooculogram (electrodes placed 1 cm above the right outer canthus and 1 cm below the left outer canthus and referred to A1), electromyogram (EMG) of the submentalis muscle (bipolar derivations with two electrodes placed 3 cm apart and affixed using a collodion-soaked gauze pad), impedance was kept less than 10 KΩ (typically <5 kΩ), EMG of the right and left tibialis anterior muscles, and ECG (one derivation). Sleep signals were sampled at 200 or 256 Hz and stored on hard disk for further analysis. The sleep respiratory pattern of each patient was monitored using oral and nasal airflow thermistors and/or nasal pressure cannula, thoracic and abdominal respiratory effort strain gauge and by monitoring oxygen saturation (pulse-oxymetry). This was performed in all subjects in a previous recording (within 1 week) or during the study recording; patients with an apnea/hypopnea index >5 were not included. Sleep stages were scored following standard criteria [7] on 30s epochs; since muscle atonia can be absent in RBD, REM sleep was scored without submental EMG atonia using electroencephalogram and electrooculogram only. According to a method specifically developed for RBD [5,8], onset of a REM sleep period was defined as the occurrence of the first rapid eye movement in the presence of an EEG signal characteristic of REM sleep (low amplitude mixed frequencies, absence of sleep spindles and K complexes). Offset of a REM sleep period was determined by the occurrence of a specific EEG feature indicative of another stage (K complex, sleep spindle, or EEG signs of arousal) or absence of rapid eye movements during 3 consecutive minutes. Epochs containing technical artifacts or extremely elevated muscle activity causing saturation of amplifiers were carefully detected and marked for exclusion from the subsequent quantitative EMG analysis.

2.3. REM sleep behavior disorder severity scale (RBDSS)

In order to classify the severity of RBD episodes we evaluated motor behavior events during REM sleep on videoPSG recordings and graded them visually and polysomnographically on an event-to-event basis, by means of the recently proposed REM sleep behavior disorder severity scale (RBDSS) [9]. According to this scale, the location of movements was categorized as follows: "0" = no visible movement; "1" = slight movements or jerks "2" = movements involving proximal extremities, including violent behavior; "3" = axial involvement including bed falls. Vocalizations were rated as "1" for present or "0" for absent. The final RBDSS score was determined by the highest score obtained in each videoPSG recording. In order to treat statistically these results we slightly modified the final score (RBDSSmod) by adding to the movement location category (0–3) the value of 0 in the absence of vocalizations or 0.5 in their presence; in this way we obtained a 8-level grading for RBDSSmod (0–3.5).

2.4. Quantification of the submentalis muscle EMG amplitude

For the computer quantitative analysis of the submentalis muscle EMG activity we used an established automatic scoring algorithm [10–12]. The submentalis muscle EMG signal was digitally band-pass filtered at 10–100 Hz, with a notch filter at 50 Hz and rectified. Subsequently, each REM sleep epoch included in the analysis was divided into 30 1-s mini-epochs. The average amplitude of the rectified submentalis muscle EMG signal was then obtained for each mini-epoch. After a noise reduction procedure [12], the values of the submentalis muscle EMG signal amplitude in each 1s mini-epoch were used to compute the percentage of values in the following 20 amplitude (amp) classes (expressed in μV): amp $\leqslant$ 1, 1 < amp $\leqslant$ 2, ..., 18 < amp $\leqslant$ 19, amp > 19. Muscle atonia is expected to be reflected by high values of the first class (amp $\leqslant$ 1), while phasic and tonic activations are expected to increase the value of the other classes [4,5,8]. As proposed in previous studies, an index summarizing in a single value the degree of preponderance of the first class was used in REM sleep: Atonia Index = amp $\leqslant$ 1/(100–1 < amp $\leqslant$ 2).

Mathematically, this index can vary from 0 (absence of mini-epochs with amp $\leqslant$ 1), i.e. complete absence of EMG atonia, to 1 (all mini-epochs with amp $\leqslant$ 1) or stable EMG atonia in the epoch. The Atonia Index correlates significantly with the percentage of epochs of REM sleep without atonia detected by the method by Lapierre and Montplaisir [5,10].

In addition, sequences of consecutive mini-epochs with values >2 μV were counted as movements. The number of these movements correlates significantly with the number of REM sleep 3 s miniepochs containing phasic EMG activity detected by the method by Lapierre and Montplaisir [5,10].

The algorithm was run blind to the condition of the subject, even though no manual modifications of the parameters is possible.

2.5. Statistical analysis

For the statistical analysis, all comparisons were performed by means of the nonparametric Mann–Whitney test for unpaired