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High leg motor activity in sleep apnea hypopnea patients: efficacy of clonazepam combined with nasal CPAP on polysomnographic variables

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Abstract The association of sleep apnea hypopnea syndrome (SAHS) with high leg activity in the same patient is a dilemma for the physician, as clonazepam, used to treat periodic leg movement syndrome (PLMS) can aggravate apneas, while nasal continuous positive airway pressure (nCPAP) can exacerbate PLMS. The present study aimed to compare nCPAP alone (n), nCPAP combined with clonazepam (n+c) and clonazepam alone (c) in patients with mild to moderate SAHS associated with high leg activity. Fourteen patients with an apnea hypopnea index (AHI) between 10 and 50 h^{-1} and a leg movement index with regard to time in bed [LMI (TIB)] > 15 h^{-1} on baseline polysomnography (b) were recorded on three consecutive nights with n, n+c and c, respectively. Leg movements were detected, using actigraphy, and were subsequently categorized into periodic, apnea- or hypopnea- related and nonperiodic movements (defined as neither periodic nor related to a respiratory event). The three treatments were successful in improving breathing [AHI b 26.1 (3.2) n 11.8 (2.4) n+c 5.0 (0.7) c 14.9 (1.8) h^{-1}], leg activity [LMI (TIB) b 39.1 (4.8) n 22.5 (4.4) n+c 23.9 (3.9) c 22.6 (3.7) h^{-1}] and sleep fragmentation [stage shift index b 37.3 (2.6) n 28.6 (1.6) n+c 25.6 (1.8) c 26.6 (1.6) h^{-1}]. All types of movements were reduced, the effect being significant for respiratory events related and nonperiodic movements. Combination therapy was more effective than nCPAP alone in reducing the AHI and in improving sleep efficiency. We conclude that in patients with mild to moderate SASH associated with high leg activity, nCPAP improves nocturnal breathing and clonazepam reduces leg activity. More unexpectedly, nCPAP is beneficial on leg activity and clonazepam on breathing, probably through a decrease in sleep fragmentation. The best results are obtained with combination therapy.

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Keywords sleep apnea hypopnea syndrome; nasal continuous positive airway pressure; periodic leg movement syndrome; clonazepam; sleep fragmentation.

INTRODUCTION

Dyssomnia, morning fatigue and daytime sleepiness are frequent symptoms in patients with sleep apnea hypopnea syndrome (SAHS). Nasal continuous positive airway pressure (nCPAP), when applied at effective level, abolishes apneas and hypopneas, increases oxyhemoglobin saturation, stabilizes sleep and usually improves symptoms. Some SAHS patients, however, remain symptomatic on domiciliary nCPAP, despite a good compliance and a dramatic decrease in their apnea hypopnea index (AHI). One possible explanation for failure of nCPAP is (1) the association with a periodic leg movement syndrome (PLMS). Periodic leg movements are repetitive and highly stereotyped movements, typically involving dorsiflexion of the big toe and ankle and sometimes also flexion of the knee and hip. They last 0.5–5 s and the intermovement interval ranges 5–90 s. They represent a potential cause for sleep disruption (2). The association of SAHS and PLMS seems a rather common finding, particularly in senior patients complaining of dyssomnia and/or sleepiness (3,4). The treatment of these two conditions in a same patient is difficult. Indeed, clonazepam is proposed as a first-line agent to treat PLMS (2,5) but is considered as contraindicated by sleep apnea (6). Conversely, nCPAP treatment for SAHS has been reported to exacerbate a pre-existing PLMS (7). Furthermore, the justification for studying only periodic

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movements may be questioned. Nonperiodic leg movements have been reported in patients with SAHS (8,9) and in patients with other sleep disorders (9) but their pathological relevance has not yet been agreed upon.

In our Sleep Unit, recording and counting of all leg movements either periodic or not, is a systematic policy. The present study was designed to prospectively evaluate the optimal strategy in patients showing the association of SAHS with high leg motor activity, in a setting of acute trial in the Sleep Unit. In each patient, three treatment modalities, namely nCPAP alone, nCPAP combined with clonazepam and clonazepam alone were, respectively, assessed on three consecutive nights. Subsequently, home treatment was prescribed by the physician on basis of the results of these three night-trials and the patients were followed up at the Chest Clinic.

METHODS

Study design

A group of subjects having SAHS combined with a high leg movement index as assessed from a baseline polysomnography were recorded in the Sleep Unit for three consecutive nights. All subjects gave informed consent after full explanation of the study protocol. On the first night, nCPAP was started at an initial pressure of 4 mbar, and then was gradually increased until most apneas and hypopneas were abolished and snoring was eliminated. On the second night, subjects were given 1 mg clonazepam 30 min before bedtime and slept on nCPAP, at an effective pressure as assessed from the first night. On the third night, they were given 1 mg clonazepam 30 min before bedtime but slept without nCPAP. The decision for home treatment was left to the discretion of the physician. All patients were followed up at the Chest Clinic.

Subjects

Fourteen outpatients were recruited to participate in this study. All had presented with one or more of the following complaints: snoring, restless sleep, morning fatigue, daytime sleepiness.

All of them showed on baseline polysomnography a mild-to-moderate SAHS, defined as an AHI between 10 and 50 h^{-1}, combined with a leg movement index (LMI) $> 15\ h^{-1}$. Patients with severe SAHS (AHI $> 50\ h^{-1}$), with medical conditions (diabetes, renal disease) or on medications (tricyclic antidepressants) known to exacerbate PLMS, were not admitted.

Polysomnography

All night polysomnography was performed using standard sleep recording leads (electro-oculogram, EEG, chin electromyogram), ECG, nasobuccal thermistor, thoracic and abdominal belts, transcutaneous oxymetry with ear probe and leg actigraphy. Sleep staging was performed according to the criteria of Rechtschaffen and Kales on 20 s epochs (10). Time in bed (TIB) was defined as the total time of recording, sleep period time (SPT) as the time from the onset of sleep to the last awakening in the morning, and total sleep time (TST) as SPT minus any time the subject was awake after falling asleep. Sleep efficiency (SE) was the ratio of TST to TIB, expressed as a percentage, and stage shift index (SSI) was the sum of all stage shifts divided by SPT, expressed as a number per hour. Rapid eye movement sleep (REMS) proportion and slow wave sleep (SWS) proportion were reported as percentages of SPT. Apnea was defined as a cessation of flow at the nose and mouth for at least 10 s. Hypopnea was scored as a decrease for at least 10 s of the amplitude of the rib cage and abdomen motion signals to less than 50% of the level prevailing before the event, coupled with a fall in oxyhemoglobin saturation ($\mathcal{S}aO_2$) of 3% or more. The AHI was calculated as the sum of all apneas and hypopneas divided by TST and expressed as a number of events per hour. The maximal duration of either apneas or hypopneas (D_{max}) was also retained for analysis. Apneas were considered as obstructive if thoracic movements persisted during the cessation of flow, and the obstructive apnea index (OAI) was calculated as the sum of all obstructive apneas divided by TST, and expressed as a number of events per hour.

The motor activity of both legs was recorded, using actigraphy, and the movements were scored visually. The number of leg movements having occurred during periods of effective sleep, divided by TST, yielded the leg movement index with regard to total sleep time [LMI (TST)] and the total number of leg movements divided by TIB yielded the leg movement index with regard to time in bed [LMI (TIB)]. Subsequently, a categorization of leg movements was made, using a specifically designed software. Movements were classified into periodic movements, according to Coleman's criteria (11), movements related to an apnea or a hypopnea, defined as occurring during post-apneic, or post-hypopneic, resumption of ventilation, and movements being neither periodic nor related to a respiratory event. All recordings were visually checked by an experienced lecturer (MK), in order to detect and to correct any erroneous categorization made by the software. Dividing the number of each type of movements by the TIB yielded, respectively, a periodic leg movement index [PLMI (TIB)], an apnea- or hypopnea-related leg movement index [AHLMI (TIB)] and a nonperiodic leg movement index [NPLMI (TIB)].

Statistical analysis

An analysis of variance with repeated measures was used. The data from the four recording nights (baseline; nCPAP; nCPAP plus clonazepam; clonazepam) were first globally analyzed to search for a possible treatment effect. If such an effect was identified, pairwise comparisons were performed between the different nights (baseline *vs* nCPAP; baseline *vs* nCPAP plus clonazepam; baseline *vs* clonazepam; nCPAP *vs* nCPAP plus clonazepam; nCPAP *vs* clonazepam; nCPAP plus clonazepam *vs* clonazepam). As usually, statistical significance was considered to be achieved when $P \leq 0.05$.

RESULTS

Patients

Fourteen patients were recruited. All but one were men. Their anthropometric features were [mean (SD)]: age 54 (12) years, height 175 (7) cm, weight 91 (18) kg, body mass index 29.6 (5.3) $kg\,m^{-2}$. Baseline polysomnography showed (Table 1) SAHS of moderate severity, mean leg movement indices around 35 h^{-1} and marked sleep fragmentation. Where breathing abnormalities are concerned, the preponderance of hypopneas was a remarkable finding, as they represented more than 50% of breathing abnormalities in all patients (70.5% on average). As the motor activity of the contralateral leg yielded no additional information, LMI (TST), LMI (TIB), PLMI (TIB), AHLMI (TIB) and NPLMI (TIB) were reported only for the left leg.

Therapeutic trial

The evolution of each variable during the three night-acute treatment trial is shown in Figs 1–3. The global treatment effect of the three night protocol reached significance, except for REMS ($P = 0.140$) and for PLMI (TIB) ($P = 0.114$). In comparison with baseline polysomnography (Table 1), nCPAP alone improved all the respiratory and some of the leg motor variables, as well as the SSI. The beneficial effect of nCPAP on periodic movements ($P = 0.084$) and on nonperiodic movements ($P = 0.077$) drew near significance. Using the same comparison with baseline, nCPAP plus clonazepam was effective in improving all the respiratory and the leg movement variables (except for periodic movements), the SE and the SSI (Table 1). The pairwise comparison clonazepam alone *vs* baseline showed a beneficial effect on the AHI, the leg motor variables (except for periodic movements), the SE and the SSI and a deleterious effect on the SWS (Table 1).

Between-treatment comparisons showed (Table 2) that combination therapy was more effective than either nCPAP alone or clonazepam alone in reducing the AHI. Where obstructive apneas are concerned, as shown in Table 2, either combination therapy or nCPAP alone was more effective than clonazepam alone. A similar difference in effectiveness was observed in reducing maximal apnea or hypopnea duration with, however, only the

Table 1. Polysomnographic variables in 14 patients with sleep apnea hypopnea syndrome associated with a high leg movement index, at baseline and during the three treatment nights

	Baseline	nCPAP	nCPAP + clonazepam	Clonazepam
AHI (h^{-1})	26.1 (3.2)	11.8 (2.4)**	5.0 (0.7)***	14.9 (1.8)**
D_{max} (s)	52.7 (4.9)	36.9 (3.4)*	32.9 (2.9)**	49.1 (5.8)
OAI (h^{-1})	4.0 (1.0)	0.3 (0.1)**	0.1 (0.1)**	3.3 (1.0)
LMI (TST) (h^{-1})	37.9 (5.3)	20.6 (5.4)*	20.5 (4.3)*	18.9 (3.7)*
LMI (TIB) (h^{-1})	39.1 (4.8)	22.5 (4.4)**	23.9 (3.9)*	22.6 (3.7)*
PLMI (TIB) (h^{-1})	21.7 (4.6)	12.3 (3.1)	16.8 (3.4)	12.9 (3.2)
AHLMI (TIB) (h^{-1})	7.3 (1.7)	2.4 (0.6)**	1.5 (0.6)**	2.6 (0.7)*
NPLMI (TIB) (h^{-1})	10.1 (1.0)	7.8 (1.2)	5.6 (1.0)**	7.1 (0.8)**
SE (%)	79.1 (2.2)	73.8 (2.7)	86.2 (1.4)*	86.1 (1.8)*
REMS (%)	14.5 (1.8)	11.9 (1.9)	15.6 (1.7)	15.9 (1.5)
SWS (%)	3.4 (0.9)	2.5 (0.9)	3.0 (1.1)	1.2 (0.5)**
SSI ((h^{-1})	37.3 (2.6)	28.6 (1.6)**	25.6 (1.8)***	26.6 (1.6)**

AHI = apnea hypopnea index; D_{max} = maximal duration of apnea or hypopnea; OAI = obstructive apnea index; LMI (TST), LMI (TIB) = leg movement index (with regard to total sleep time) (with regard to time in bed); PLMI (TIB), AHLMI (TIB), NPLMI (TIB) = periodic leg movement index, apnea or hypopnea related leg movement index, nonperiodic leg movement index (with regard to time in bed); SE = sleep efficiency; REMS = proportion of rapid eye movement sleep; SWS = proportion of slow wave sleep; SSI = stage shift index. Data in the table are mean (SEM) values.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ for pairwise comparison of each treatment night with baseline.

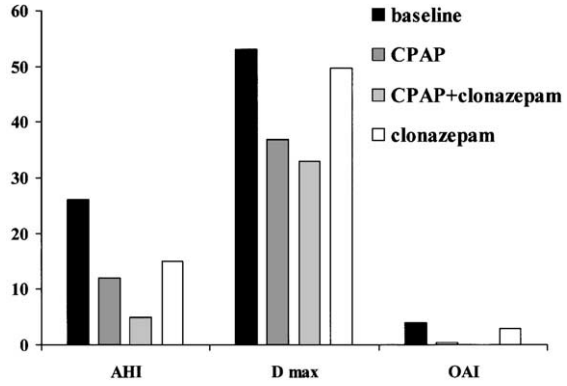

Fig. 1. Mean values of respiratory variables in 14 patients with sleep apnea hypopnea syndrome associated with high leg motor activity. Baseline, nCPAP alone, nCPAP plus clonazepam and clonazepam alone are represented, respectively, as black, heavy gray, light gray and white columns. AHI = apnea hypopnea index, D_{max} = maximal duration of apnea or hypopnea, OAI = obstructive apnea index.

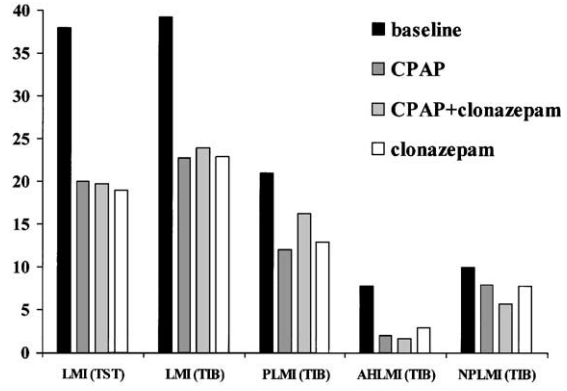

Fig. 2. Mean values of leg motor activity variables in 14 patients with sleep apnea hypopnea syndrome associated with high leg motor activity. Otherwise same legend as Fig. 1. LMI (TST), LMI (TIB) = leg movement index (with regard to total sleep time) (with regard to time in bed), PLMI (TIB), AHLMI (TIB), NPLMI (TIB) = periodic leg movement index, apnea or hypopnea related leg movement index, nonperiodic leg movement index (with regard to time in bed).

difference between combination therapy and clonazepam alone reaching significance. Where leg activity is concerned, combination therapy was more effective than clonazepam alone in reducing movements related to respiratory events. Finally, either combination therapy or clonazepam alone was more effective than nCPAP alone in increasing SE (Table 2).

Clinical management

Ten out of 14 patients were prescribed combined therapy at home, while four patients were given nCPAP alone. Out of these 10 patients on combined therapy, seven did well (median follow-up of 24 months) with, however, a need to reduce the dose of clonazepam to 0.5 mg in two subjects. Two subjects did not tolerate nCPAP, were subsequently treated by clonazepam alone, and finally did well. One patient did not tolerate clonazepam and finally did well on nCPAP alone. Out of the four patients on nCPAP alone, two did well while two did not tolerate nCPAP.

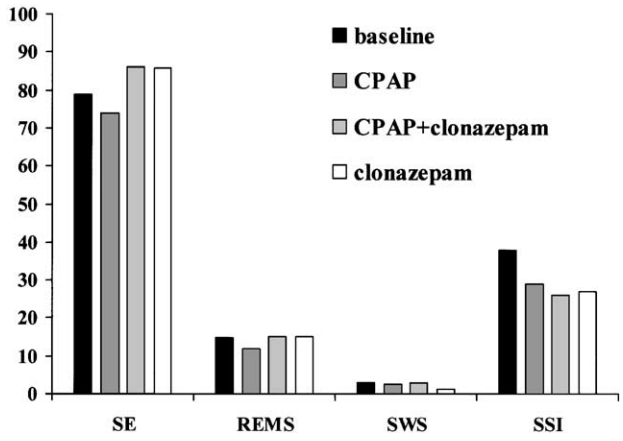

Fig. 3. Mean values of sleep variables in 14 patients with sleep apnea hypopnea syndrome associated with high leg motor activity. Otherwise same legend as Fig. 1. SE = sleep efficiency, REMS = proportion of rapid eye movement sleep, SWS = proportion of slow wave sleep, SSI = stage shift index.

DISCUSSION

The association of SAHS with high leg motor activity in the same patient represents both a diagnostic problem and a therapeutic dilemma for the physician. Firstly, the real significance of high leg activity is not clear. Usually, periodic movements are considered to be a potential cause for sleep disruption (2) while the significance of leg movements that are not periodic is largely unknown. However, the traditionally used classification for periodicity accepts intermovement intervals between 5 and 90 s; as a consequence, the so-called periodic movements include, in fact, a large heterogeneity of movement patterns. In the present study, we detected leg movements using actigraphy—a method which has been validated (12)—and we decided to score all movements, whatever periodic or not. Secondly, where therapy is concerned, clonazepam—one of the most used agents to treat PLMS (2)—belongs to the class of the benzodiazepines, which are usually considered to be contraindicated in the presence of SAHS. This notion is based both on experimental evidence as diazepam depresses the motor activity of upper airway muscles in the decerebrate cat (13), and as triazolam increases the arousal threshold to airway occlusion in patients with severe

Table 2. Analysis of variance with pairwise comparison between treatment nights, in 14 patients with sleep apnea hypopnea syndrome associated with a high leg movement index

	nCPAP + clonazepam/nCPAP	Clonazepam/nCPAP	Clonazepam/nCPAP + clonazepam
AHI	0.005	0.322	<0.001
D_{max}	0.302	0.083	0.013
OAI	0.342	0.008	0.006
LMI (TST)	0.989	0.767	0.681
LMI (TIB)	0.722	0.987	0.683
AHLMI (TIB)	0.161	0.739	0.040
NPLMI (TIB)	0.104	0.528	0.139
SE	<0.001	0.002	0.967
SWS	0.593	0.045	0.058
SSI	0.090	0.193	0.625

Data in the table are *P* values. See Table 1 for meaning of abbreviations.

SAHS (14) and on clinical experience showing that flurazepam can induce apneas in normal subjects (15), particularly in the elderly (16). Conversely, nCPAP — largely considered as the treatment of choice for SAHS — can exacerbate PLMS (7). It has been hypothesized that, in SAHS patients, the PLMS may be disguised until apnea is treated (1), but the inadvertent application of nCPAP in a patient without sleep apnea has been reported to induce PLMS, suggesting a role of nCPAP itself (17). In clinical practice, it is often considered a priority to treat SAHS, as it is a condition associated with significant mortality (18) while excessive leg motor activity is considered as benign and is therefore neglected when it is associated with SAHS. However, some SAHS patients still complain of dyssomnia, morning fatigure and daytime sleepiness when adequately treated by nCPAP at home. In our experience as in that of others (1), the coexistence of PLMS is a common finding in these subjects and appropriate treatment with clonazepam may be effective in improving symptoms in at least some of these subjects.

The present study aimed at comparing patients with combined SAHS and high leg motor activity nCPAP alone, nCPAP plus clonazepam and clonazepam alone in an acute trial in the Sleep Unit over three consecutive nights. This study has several limitations. Firstly, the three modes of treatment were not randomized. We considered that it was inappropriate to administer clonazepam, either alone or combined with nCPAP, on the first night and to withdraw it on the second night, as acute withdrawal of a benzodiazepine agent may induce or exacerbate dyssomnia. That is why a fixed successive design was used, with clonazepam given on the second and third nights. Secondly, it may be argued that, as the first night consisted in a nCPAP titration procedure, the subjects slept during the initial part of this first night at suboptimal pressure, which could bias the comparison between the first (nCPAP alone) and the second night (nCPAP plus clonazepam) in favor of the latter one. However, a large between-subject variability in the time needed to reach the effective pressure prevented us from taking into account solely that part of the first night where the optimal pressure had been reached. Thirdly, it may be questioned whether — during the third night — there was some residual effect of nCPAP, applied during the two preceding nights. The beneficial effect of nCPAP has indeed been shown to persist for some time when the mask is off, partly because of a decrease in mucosal edema in the upper airway (19). However, this decrease in edema is obtained only after several nights on nCPAP and is very unlikely to be involved in an acute trial setting.

In comparison with baseline polysomnography, nCPAP improved nocturnal breathing and clonazepam decreased leg movements, as expected. More unexpectedly, nCPAP was effective in reducing leg motor activity and clonazepam significantly reduced the AHI. The categorization of leg movements into periodic movements, movements related to respiratory events and nonperiodic movements allowed us to refine the analysis of treatment effects. We found that the movements related to apneas or hypopneas decreased with the three treatments and that both clonazepam and combination therapy reduced the nonperiodic movements, while the periodic movements were poorly influenced by the treatment protocol (except for a beneficial trend with nCPAP alone). Again, the beneficial effect of nCPAP on respiratory events related movements was an expected finding, while that of clonazepam on the same type of movements was much more unexpected. An unifying explanation for the unexpected benefits obtained with nCPAP (on leg motor activity) and with clonazepam (on breathing) is a beneficial effect mediated by stabilizing

sleep. Indeed, it is well known that apneas and hypopneas disrupt sleep, but conversely sleep fragmentation itself can be the primary element in repetitive abnormal breathing pattern (20). Similarly, leg movements can disrupt sleep, but conversely a poor sleep architecture, with REMS and SWS deficiency, can favor leg movements (21). In the particular population studied, here characterized by apneas and—predominantly—hypopneas, associated with high leg motor activity, an improvement in sleep continuity may, whatever be its cause, have resulted in less respiratory events and less motor events. The observation that clonazepam alone reduced the overall number of respiratory events, but not the obstructive apneas, supports this interpretation. Even more supportive for this interpretation is the observation that periodic movements showed a trend to decrease with nCPAP and that apnea- or hypopnea-related movements decreased with clonazepam.

The results of this study, performed in a clinical setting, suggest that it may be useful to add clonazepam to nCPAP in a patient having an excessive leg motor activity associated with moderate SAHS. The expected benefits from combined therapy are an additional improvement in the AHI and an increase in sleep efficiency. However, with the acute trial design used in the present study, the first night with nCPAP often does not demonstrate, as discussed hereinabove, the full effect of this treatment, and the better results obtained with nCPAP plus clonazepam could be due, at least partly, to a second night effect rather than to the addition of clonazepam. Whether the improvement in sleep on combined therapy, compared with nCPAP alone, is sustained during long-term home therapy and whether this improvement adds to the quality of vigilance of the patients remains to be demonstrated. The usual statement that benzodiazepine agents are contraindicated in any patient with SAHS (6) is possibly an overstatement. Some recent studies have indeed shown that nitrazepam e.g. does not worsen sleep apnea in patients with-mild-to-moderate SAHS (22). The present study shows that a 1 mg dose of clonazepam, associated with nCPAP, is safe and beneficial in patients with moderate SAHS and high leg motor activity. Our results also suggest that a 1 mg dose of clonazepam alone is deleterious for the SWS but is safe where breathing is concerned, at least in the very short term. These results should not be extrapolated to patients with severe SAHS. The present study should be considered, in view of its methodological limitations, as a preliminary investigation. In further research, a three night acute trial design could be improved by telling the subjects that combined therapy is given on all nights and by adding an oral placebo (first night) and a sham nCPAP (third night). Alternately, subjects on maintenance therapy with nCPAP for some weeks could be studied at the Sleep Unit with the addition of either an oral placebo or clonazepam.

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