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Novel Therapeutic Approach for Parkinson Disease during REM Sleep

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Abstract

Study objectives: The physiological responses of an individual depend on preset limits. They must be able to adapt it to changing environmental conditions, modifying the thresholds. We propose a regulatory function of biological responses during REM sleep. Responses previously developed during wakefulness, are evaluated and regulated for integration into the repertoire of responses during sleep. The aims of this study were to evaluate the impact of the restoration of REM sleep in patients with Parkinson disease by stimulation of D2 receptors and to evaluate the symptomatic benefit of this approach.

Methods: Ten parkinsonian patients underwent a polysomnography study using nocturnal apomorphine subcutaneous administration at the beginning of each REM detected along all night recording.

Results: This therapeutic approach led to a significant benefit for patients in all of three UPDRS scores. The mean UPDRS III motor examination "On" scores (mean ± SD) were reduced by 9.4 ± 8.5 points ($p<0.0001$). For patients in the UPDRS II scores a total difference of 12 ± 4.22 to 5.2 ± 5.22 ($p<0.0001$) were observed; and in total UPDRS I the difference was of 5.2 points ($p<0.0001$), with a reduction from 8.4 ± 3.2 to 3.2 ± 3.1.

Conclusion: Sleep alteration can be improved by stimulation of D2 receptors. The symptomatic benefits obtained linked to the restoration of REM functions in patients with PD were significant.

Keywords: Parkinson disease; Sleep; Receptors

Introduction

Neurodegenerative diseases are often characterized by a progressive deterioration in the regulation of motor, cognitive or psychiatric responses and decreasing response to currently available treatments. However, the way of progression and the extent of engagement are not always the same, and different factors can be decisive in the course and prognosis of the disease. The most resilient individuals might have better resources to deal with the high allostatic load generated by all these chronic diseases. We know that neuroplasticity depends on adequate cellular resilience, which promotes neurogenesis and sprouting; and these are determined by genetic and environmental factors. The latter can be an important target to future therapeutic options.

Sleep is responsible for different functions necessary for homeostasis. During normal aging sleep is reduced and fragmented, and this is even more pronounced in neurodegenerative disorders. This disturbed sleep-wake rhythm is probably related to circadian dysregulation appears during normal aging and in a more sharply way in Alzheimer disease (known as hyper-aging) [1]. Some studies have shown that good sleep quality could have a protective effect in those genetically susceptible individuals (APOE genotypes related) to develop Alzheimer's disease [2] decreasing even the associated neuropathological changes [3].

Sleep develops in a cyclic fashion between two markedly different states, rapid eye movement (NREM) sleep and (REM) sleep. The latter, is characterized by a mixed frequency electroencephalographic activity (theta and faster rhythms) which arise from bidirectional interactions of cortical, hippocampal, and subcortical networks [4,5]; and the ponto-geniculo-occipital (PGO) waves [6,7]. Functionally efficient REM sleep is characterized by high dopaminergic activity (DA). It was reported a reduction or even suppression of REM sleep with dopamine D2 receptor blocking after a period of REM sleep deprivation (REMSD) [8], with down-regulation of D2. The receptor role in REM regulation has also been tested in the dopaminergic transporter knockout (DAT-KO) mice where selective activation of D2 receptors, but not D1, allows the recovery of REM sleep [9]. In another study striatal DA release is strongly enhanced by the selective agonist D2 piribedil, even more marked with REMSD [10].

Dopaminergic neurons in the ventral tegmental midbrain (VMT) are an active regulator of sleep and wakefulness states, particularly during REM sleep [11]. Glutamatergic and cholinergic neurons of the tegmental pontomesencephalic (TPM) by excitatory stimuli on the dopaminergic neurons of the ventral tegmental area (VTA) achieve maximum activity during REM sleep by changing their own discharge pattern [12-14], generating an increased calcium influx and other signals that stimulate immediate early gene expression [15].

Objective

It is possible that dopaminergic deficit is one of the factors involved in the circadian dysregulation that occurs with neurodegenación. In Parkinson's disease (PD) is usually observed a reduction of REM sleep as result of the alterations described before. To assess whether the restoration of the functions of REM may improve symptoms of Parkinson's disease a study was conducted with polysomnographic control, where patients with this disease was administered a dose of a dopamine agonist at the beginning of each REM overnight. apomorphine (APO) was chosen for its rapid onset of action and short effect, applied subcutaneously. It is a potent agonist of D1 and D2 receptors. Its high lipid solubility leads to transient brain concentrations, which can be up to eight times higher than plasma [16,17].

Patients and Methods

Patients

The study was conducted by the Department of Neurology at the Fides Center in Jujuy, Argentina. From May 2014 to January 2015, 10 consecutive patients with Parkinson's disease were recruited to take part in this observational study. Patients met the criteria for definite idiopathic Parkinson's disease [18]. All participants gave written informed consent for the protocol, which was approved of by the local ethics committee.

The following efficacy and safety outcomes were assessed: Unified Parkinson's Disease Rating Scale (UPDRS) parts I, II, III and IV. Complications of therapy (UPDRS IV: Items 32 and 39 were applied according to the Movement Disorder Society-UPDRS), activities of daily living (UPDRS II), motor performance (UPDRS III), both assessed at the "On" state. Patient reported QoL (quality of life) using disease-specific Parkinson's disease Questionnaire short version with 8 items (PDQ-8). To assess safety of this approach, all adverse drug reactions (ADR) were recorded. ADR were defined as adverse events reported by the investigator as "unlikely," "possibly," or "probably" related to the study drug system. Data were recorded at baseline (BL) prior to initiation of treatment (nocturnal apomorphine application), at day 1 (D1), and at follow-up visits 7 days (7D) and 1 month (M1) thereafter. UPDRS I, II, III and IV data were summarized with descriptive statistics. QoL data were analyzed according the validated standard procedures (PDQ-8). Paired t-tests were used for statistical testing of efficacy and QoL data comparing BL with D1, D7, and M1.

Clinical evaluation

Data about demographic characteristics, medical history, Parkinson's disease course and treatment were collected during a face-to-face interview. In addition, patients were interrogated about their sleep habits during the current year. Sleep was monitored during a single nigh. Patients came to the sleep laboratory in the afternoon, and were instructed to take their levodopa and dopamine agonists as usual. The monitoring included a standard electroencephalography, right and left electro-oculogram, nasal pressure through a cannula, tracheal sounds through a microphone, thoracic and abdominal belts to assess respiratory efforts, electrocardiography, pulse oximetry, EMG (levator menti, carpi radialis and tibialis anterior muscles) and EEG-synchronized infrared video-monitoring. The sleep stages, arousals, alpha rhythm on EEG, respiratory events, periodic leg movements and muscle activities were scored through visual inspection according to standard criteria and definitions previously reported.

The study was developed on the basis of nocturnal subcutaneous administration of 2 mg of apomorphine at the beginning of each REM detected along all night recording or at regular intervals at the right time in those cases that this stage does not appear; preceded by the application of an initial single oral dose of 20 mg of domperidone.

Results

The mean age was 68.5 years. Baseline assessments of motor and non-motor symptoms are presented in Table 1. A majority of patients was on one or more additional antiparkinsonian drugs, mainly IMAO inhibitors and DAs (Table 1). At the start of the study, all the patients were using oral levodopa, and approximately 70% were using other anti-PD medications.

Demographics	
Gender	
Female	8 (80%)
Male	2 (20%)
Age (years)	68.5
<65 years	2 (20%)
≥ 65 years	8 (80.0%)
Medical history	
Time since PD diagnosis (years)	5
Dementia	20 (11.7%)
PD symptoms and QoL measures at baseline	
UPDRS I	8,4 ± 3.2
UPDRS II (activities of daily living) at "On" state	12 ± 4.2
UPDRS III (motor examination) at "On" state	25.3 ± 7.5
Non-Motor Symptoms Scale (NMSS total score)	75.3 ± 42.2
Previous PD medication as reported at baseline	
Levodopa	10 (100%)
Dopamine agonist	3
COMT inhibitors	1
MAO-B inhibitors	2
Amantadine	1
Other oral medications	0

Table 1: Baseline patient demographics and disease characteristics. Data presented in mean ± standard deviation (SD) or number (%). Parkinson's disease (PD), Unified Parkinson's Disease Rating Scale (UPDRS), Non-Motor Symptoms Scale (NMSS), Parkinson's Disease Questionnaire – 8 item (PDQ-8), Catechol O-methyl transferase (COMT), Monoamine oxidase-B (MAO-B).

In all UPDRS domain the major difference was found at 7-D. The most significant results were obtained with the UPDRS III motor examination scores. The mean UPDRS III motor examination "On" scores (mean ± SD) were reduced by 9.4 ± 8.5 points (p<0.0001). The mean UPDRS item 18 speech was reduced from 1.3 ± 0.82 at BL to 0.4 ± 0.7 (p<0.0001). UPDRS item 22 (Rigidity): -0.7 ± 0.48, p=0.001, item 23 (Finger taps): -0.7± 0.82, p=0,001, Hand movements: -0.8 ± 0.47, p=0.0002, Bradykinesia: -0.9 ± 1.26 (p<0.0001) and constancy of rest tremor: from 2.2 ±0.81 to 1.3 ± 0.73 (p<0.0001).

In addition, significant benefit was observed for patients in the UPDRS II scores with a total difference of 12 ± 4.22 to 5.2 ± 5.22 (p<0.0001). The mean item 7 chewing and swallowing was reduce from 1 ± 0.47 to 0.3 ± 0.48 (p=0.001), Cutting food and handling utensils: from 1 ± 0.47 to 0.3 ± 0.48 (p=0.001), Turning in bed: from 1.1 ± 0.31 to 0.3 ± 0.48 (p=0.0002). Walking and balance from 1.2 ± 0.63 to 0.5 ± 0.52 (p=0.001), getting out of bed, car or deep chair from 1.4 ± 0.69 to 1 ± 0.82 (p=0.04). Finally tremor showed a difference for 0.6 ±0.51 (p=0.005). A smaller but significant improvements of non-motor symptoms were observed in 3 out of the 10 NMSS domains (Intellectual impairment: from 1.2 ± 0.91 at BL to 0.6 ± 0.7 (p=0.0002). With a difference in total UPDRS I of 5.2 points (p<0.0001), with a reduction from 8.4 ± 3.2 to 3.2 ± 3.1. Other domains that showed improvement were depression: from 1.2 ± 0.63 to 0.3 ± 0.48 (p=0.0007), Motivation/initiative: from 1 ± 0.8 to 0.2 ± 0.63 (p=0.0002).

PDQ-8 scores (mean ± SD) significantly improved at follow-up with a maximum reduction of -3.8 ± 1.8 at M1 (p=0.0001). In 3 out of the 8 PDQ-8 items QoL improvements were observed at M1: item 3 (felt depressed: -0.9 ± 2, p=0.0007), item 2 (had difficulty dressing yourself: -0.7 ± 2.2, p=0.001), and item 5 (had problems with your concentration: -0.5 ± 2, p=0.01). No ADR were observed, except for nausea in two of them.

Discussion

This is the first time, to our knowledge, that a therapeutic approach during REM sleep is carry out in patients with Parkinson's disease. Studies with overnight apomorphine applied in continuous infusion and one with patches were made to treat nocturnal symptoms of Parkinson and restless legs syndrome [19,20]. In none of them the effects on daytime symptoms was an end point and even more, none of these was designed with the aim of assessing the benefit of dopaminergic D2 agonism in REM stage. The results obtained are consistent with the concept that sleep disorders, particularly in REM stage, occur frequently in patients with dopaminergic neurodegeneration. The hypothesis of the potential neuromodulator effect of sleep on biological functions must still be confirmed by further studies. But some conclusions can be drawn from the results thrown here.

The dopaminergic deficit causes a significant decrease of REM sleep. This alteration can be corrected, at least partly by stimulation of D2 receptors. In patients undergoing this study, REM stage developed normally once subcutaneous apomorphine was administered; or it was induced, in cases where REM was not observed 40 minutes after the expected time. The overall symptomatic benefits in patients with PD were significant and can only be linked to the restoration of REM functions, given the protocol used, where the added dopaminergic effect was limited only to this stage of sleep.

The above results suggest a beneficial therapeutic effect with dopaminergic replenishing during the time of greatest neuronal plasticity. This supports the hypothesis that REM sleep is a period for reprogramming responses, a state where the limits and control of certain functions can be moved to a new state of equilibrium. The lack of control and the small population used are some important limitations of this study. New and more comprehensive research are needed to determine the role of this therapy in PD and other degenerative diseases, as well as longer monitoring, to define the optimal frequency of this type of approach (Figures 1-4).

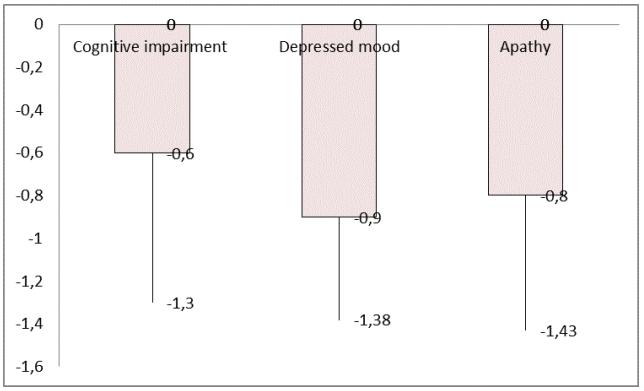

Figure 1: Unified Parkinson's disease Rating Scale (UPDRS) I. Mean change from baseline at D7 after nocturnal apomorphine application. Bars are standard deviation. Compared to baseline from paired t-test.

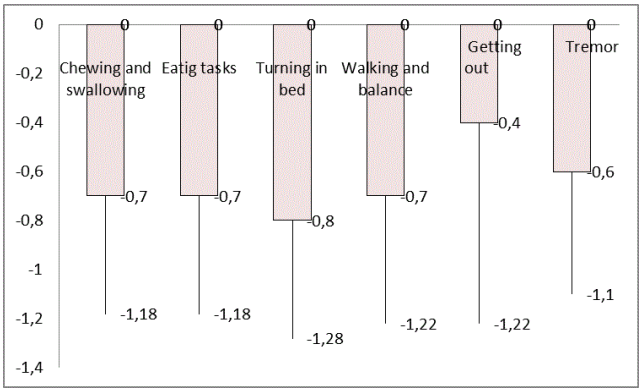

Figure 2: Unified Parkinson's disease Rating Scale (UPDRS) II. Mean change from baseline at D7 after nocturnal apomorphine application. Bars are standard deviation. Compared to baseline from paired t-test.

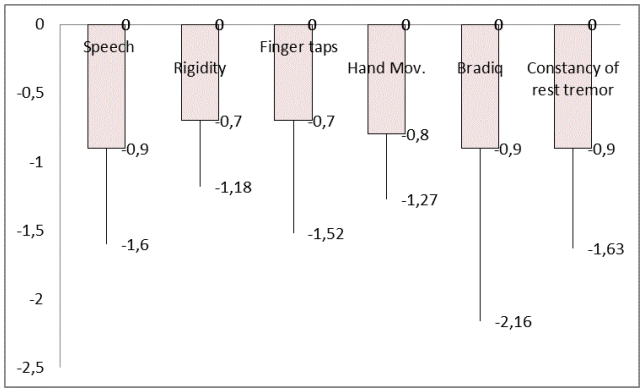

Figure 3: Unified Parkinson's Disease Rating Scale (UPDRS) III. Mean change from baseline at D7 after nocturnal apomorphine application. Bars are standard deviation. Compared to baseline from paired t-test.

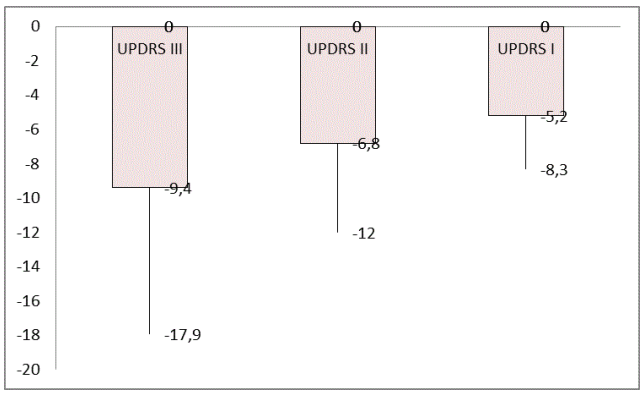

Figure 4: Total UPDRS scores results. Mean change from baseline at D7 after nocturnal apomorphine application. Bars are standard deviation.

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