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Nocturnal anomalous movement reduction and sleep microstructure analysis in parkinsonian patients during 1-night transdermal apomorphine treatment

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Abstract This study analyzed the macrostructure and microstructure of sleep in 12 parkinsonian patients under basal conditions (T0) and during 1-night treatment (T1) with a new formulation of apomorphine. This new formulation consisted in a microemulsion of apomorphine administered by the transdermal route, able to provide a constant release of the drug over several hours (APO-TD). Sleep analysis at T1 compared with T0 revealed a 16% increment of total sleep time, a 12% increment of sleep efficiency, a 16% increment of stage 3 and 4 non-REM sleep, a 15% reduction of periodic limb movements index, a 22% reduction of arousal index, and a 23% reduction of cycling alternating patterns/non-REM. We conclude that APO-TD may be able to reduce nocturnal anomalous movements, akinesia, and rigidity in Parkinson's disease, and may reduce the disturbed sleep typical of Parkinson's disease.

Introduction

Sleep in Parkinson's disease is frequently disrupted. There may be several anomalous movements, such as periodic limb movements (PLMs), persistence of tremor and prolonged tonic contractions of limb muscles during non-REM sleep, prolonged elevations in muscle tone during REM sleep, REM behavior disorders, and reduction of normal body shifts during sleep. These sleep disorders may lead to awakening and microarousal, and may cause sleep fragmentation and excessive daytime somnolence [1, 2]. Analysis of sleep microstructure, including cycling alternating patterns (CAP), may provide an index of sleep maintenance and is an objective measure of disruption of sleep [3, 4].

The aim of this study was to analyze the anomalous movements during sleep and the alterations of sleep microstructure (CAP sequence analysis, microarousals) in a group of parkinsonian patients during 1-night treatment with a new formulation of apomorphine. This new formulation is a microemulsion-based drug delivery system, administered by an epicutaneous-transdermal route (APO-TD). This formulation provides a constant release of the drug for several hours, as demonstrated in vitro with hairless mouse skin [5], and may become particularly useful for night treatment of motor fluctuation in parkinsonian patients.

Materials and methods

We selected 12 consecutive patients with idiopathic Parkinson's disease, according to the following inclusion criteria: age between 55 and 75 years, stage III–IV Hoehn-Yahr, presence of long-term L-dopa syndrome characterized by "wearing-off" or predictable "off" periods, and a positive response to subcutaneous apomorphine test without severe side effects. The mean age was 62.3 years, the mean duration of illness 6.3 years, and the mean Hoehn-Yahr stage 3.2. The daily mean L-dopa dosage was 584 mg.

The patients underwent standard polysomnography under basal conditions (T0) and during nocturnal treatment with 50 mg of APO-TD applied to a 100-cm^2 cutaneous area on the chest, from 10 p.m. until 8. a.m. (T1). During this period blood samples were collected at 3-h intervals from 10 p.m. for 12 h. The apomorphine concentration was then analyzed by high-performance liquid chromatography. Anomalous sleep movements, and macrostructure and microstructure of sleep were analyzed; CAP rate (total CAP time/total non-REM time) was calculated.

Results

Pharmacokinetic analysis confirmed the absorption of apomorphine and the maintenance of therapeutic plasma levels for several hours (mean C_{max} 31.8±9.7 ng/ml, mean T_{max} 3.1±1.6 h, mean half-life absorption 1.2±1.4 h, mean half-life of elimination 8.8±1.9 h).

Sleep macrostructure analysis at T1 compared with T0 showed a 5% reduction of sleep onset latency (not significant), a 16% increment of total sleep time (p=0.03), a 12% increment of sleep efficiency (p=0.04), and a 16% increment of stage 3–4 non-REM duration (p=0.04). In contrast, no variation of stage 1–2 non-REM and REM phase duration was noticed.

Persistence of tremor and prolonged tonic contractions of limb muscles during non-REM 1–2 sleep stages were present in a high percentage of patients (75% and 83.3%, respectively). All patients showed a reduction of these disorders at T1 compared with T0, although statistical significance was not reached; 66.6% of patients presented PLMs. In these

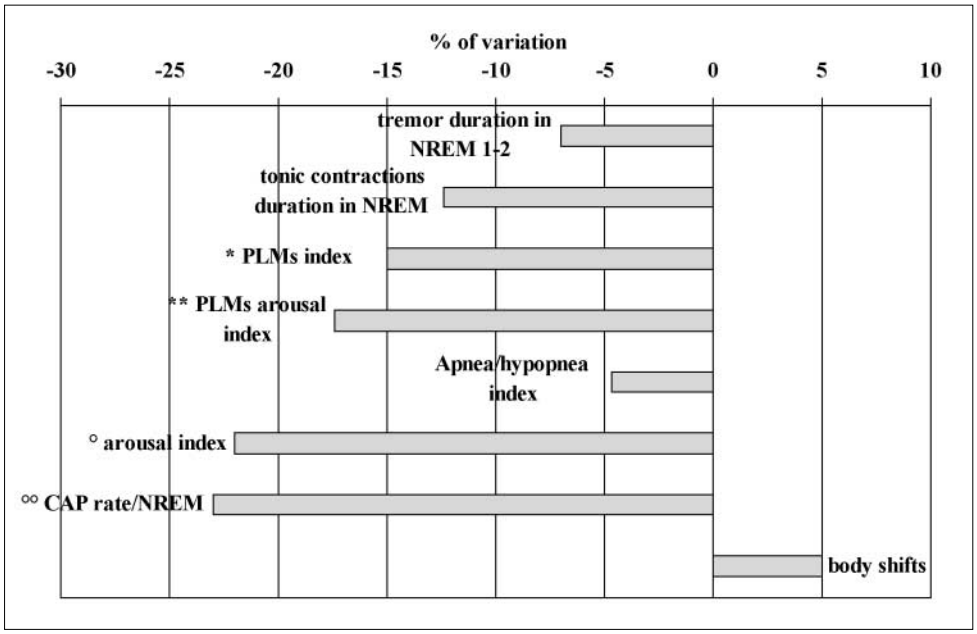

Fig. 1 Nocturnal anomalous movements reduction and sleep microstructure analysis during APO-MT treatment (T1) compared to basal condition (T0). **p*= 0.03; ***p*=0.02; °*p*=0.03; °°*p*=0.01

patients, the PLMs index and the PLMs index associated with arousals showed a significant reduction at T1 compared with T0 (15%, p=0.03 and 17%, p=0.02, respectively). Apnea/hypopnea index was below 5 at T0 in all patients, and did not show any significant variation at T1. Interestingly, during APO-TD treatment, arousal index and CAP rate/non-REM showed a significant reduction (22%, p=0.03 and 23%, p=0.01, respectively). Body shifts appeared to be increased (5%), but this variation did not reach statistical significance. In our study APO-TD overall tolerability was good. No hallucinations, vivid dreams, or nightmares occurred. Only 1 patient on awakening the following morning presented transient nausea controlled with domperidone. Five patients had a transient mild erythema at the site of APO-TD application, with complete regression within 48 h.

Discussion

Our study suggests that APO-TD treatment during the night may reduce anomalous sleep movements in Parkinson's disease. In our group of patients, persistence of tremor and prolonged tonic contractions of limb muscles during non-REM sleep were reduced, while body shifts were increased. This may be due to the prolonged dopaminergic stimulation provided by APO-TD, with a reduction of akinesia and rigidity during the night hours. Similarly the PLMs index showed a significant decrease, thus reducing one of the possible sources of broken sleep, as demonstrated by the reduction of the PLMs index associated with arousals.

This improvement of motor conditions during sleep may explain the significant decrease in the arousal index and CAP rate/non-REM, and the significant increment of sleep stage 3–4 non-REM and sleep efficiency. In particular, the CAP rate/non-REM decrease may be considered an objective index of the reduction of sleep instability in these patients.

In conclusion, our study suggests that nocturnal transdermal slow-release apomorphine treatment in Parkinson's disease, giving a constant absorption of the drug for at least 12 h, may be able to reduce nocturnal anomalous movements, akinesia, and rigidity. Hence it may be efficacious in reducing sleep instability typical of the fragmented parkinsonian sleep.

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