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Quantitative demonstration of the efficacy of night-time apomorphine infusion to treat nocturnal hypokinesia in Parkinson's disease using wearable sensors

Roongroj Bhidayasiri [a, b, *], Jirada Sringean [a], Chanawat Anan [a], Kamolwan Boonpang [a], Chusak Thanawattano [c], K. Ray Chaudhuri [d]

[a] Chulalongkorn Center of Excellence for Parkinson's Disease & Related Disorders, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, 10330, Thailand
[b] Department of Rehabilitation Medicine, Juntendo University, Tokyo, Japan
[c] Biomedical Signal Processing Laboratory, National Electronics and Computer Technology Center (NECTEC), Pathumthani, Thailand
[d] The Maurice Wohl Clinical Neuroscience Institute, King's College London and National Parkinson Foundation Centre of Excellence, King's College Hospital, London, United Kingdom

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ABSTRACT

Background: Nocturnal hypokinesia/akinesia is one of the common night-time symptoms in patients with Parkinson's disease (PD), negatively affecting quality of life of patients and caregivers. The recognition of this problem and treatment options are limited in clinical practice.
Objectives: To evaluate the efficacy of nocturnal apomorphine infusion, using a wearable sensor, in patients who are already on daytime continuous subcutaneous apomorphine infusion and still suffer from nocturnal hypokinesia.
Methods: Nocturnal parameters in 10 PD patients before and during nocturnal infusion were assessed over two nights at their homes, using a wearable sensor (trunk). Nocturnal parameters included number, velocity, acceleration, degree, and duration of rolling over, and number of times they got out of bed. Correlations with validated clinical rating scales were performed.
Results: Following nocturnal apomorphine infusion (34.8 ± 6.5 mg per night), there were significant improvements in the number of turns in bed ($p = 0.027$), turning velocity ($p = 0.046$), and the degree of turning ($p = 0.028$) in PD patients. Significant improvements of Modified Parkinson's Disease Sleep Scale ($p = 0.005$), the axial score of Unified Parkinson's Disease Rating Scale ($p = 0.013$), and Nocturnal Akinesia Dystonia and Cramp Scale ($p = 0.014$) were also observed.
Conclusion: Our study was able to demonstrate quantitatively the efficacy of nocturnal apomorphine infusion in PD patients with nocturnal hypokinesia and demonstrated the feasibility of using wearable sensors to yield objective and quantifiable outcomes in a clinical trial setting. More studies are needed to determine the long-term efficacy of this treatment in a large prospective cohort of PD patients.

1. Introduction

Noctunal hypokinesia or akinesia is a condition where individuals have difficulty in moving their body during sleep so that rolling over or turning in bed and getting out of bed is restricted [1]. Its manifestations primarily involve poor axial rotation, whole body bradykinesia, postural instability, and axial rigidity [2]. It is a common night-time manifestation affecting at least 50% of patients with Parkinson's disease (PD), that impairs both sleep quality and quality of life (QOL) of patients and poses a significant burden for caregivers [3–5]. Unfortunately this problem is often neglected in clinical practice and lack of treatment can result in serious consequences for patients, including the development of pressure ulcers, predisposition to aspiration pneumonia, and asphyxia, which can be fatal in PD patients [6,7]. Although the mechanism underlying nocturnal hypokinesia is likely to be complex, several lines of

* Corresponding author. Chulalongkorn Center of Excellence for Parkinson's Disease & Related Disorders, Chulalongkorn University Hospital, 1873 Rama 4 Road, Bangkok 10330, Thailand.
E-mail address: rbh@chulapd.org (R. Bhidayasiri).

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evidence support the presence of a low nocturnal dopamine level (similar to an off-state) as a major contributing factor [3,8]. Nocturnal hypokinesia is viewed as the longest 'off' period of all wearing-off symptoms which emphasizes the need to utilize a 24-hr or a near-24-hr treatment strategy to effectively control both day- and night-time symptoms [3,9].

Although nocturnal hypokinesia may be present throughout the night in PD patients, one might predict it would get worse as the night progresses. This suspicion was recently confirmed by our sensor-based study demonstrating significantly fewer turns in bed during the latter half of the night when compared to the first half of the night in moderate stage PD patients [10]. This finding has significant therapeutic implications as it suggests that continuous dopamine replacement throughout the night is required to achieve a sustained therapeutic benefit, especially in the second half of the night [11]. Simply adding a single dose of dopaminergic medication at bedtime is unlikely to be adequate to abolish the symptoms of nocturnal hypokinesia as shown by a lesser benefit of controlled-release levodopa in the treatment of early morning off than other nocturnal disabilities [12,13]. To test the viability of continuous dopaminergic delivery, a number of clinical trials have been conducted in advanced PD patients by giving continuous infusion of either levodopa carbidopa intestinal gel (LCIG) or apomorphine during the night with outcome measures being assessed via sleep diaries, the Modified Parkinson's Disease Sleep Scale (PDSS-2), sleep questionnaires, and related clinical rating scales [14–16]. Significant improvements in various sleep domains, including nocturnal 'off' periods, pain, dystonia, nocturnal awakening, and sleep quality support the use of nocturnal infusion for the treatment of nocturnal hypokinesia and related disabilities. However, these outcomes are based on clinical interviews in which many nocturnal symptoms can be overlooked, and do not objectively determine the ability to turn in bed, which is the major manifestation of nocturnal hypokinesia [11,17]. With the advances in sensor technology, the NIGHT-Recorder, which is an inertial sensor that is capable of giving continuous data on axial rotation of PD patients while in bed, and has been shown to provide an accurate and reliable assessment of nocturnal hypokinesia in both PD patients and controls [1,18]. Therefore, by using the NIGHT-Recorder, this study has sought to determine if an extension of daytime continuous subcutaneous apomorphine infusion (CSAI) into the night-time will objectively improve nocturnal hypokinesia in advanced PD patients with subjective complaints of impaired bed immobility.

2. Patients and methods

2.1. Patient inclusion and rating scales

Participants in this study were PD patients at Chulalongkorn Center of Excellence for Parkinson's Disease & Related Disorders (www.chulapd.org) with the diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank criteria, and who were already under daytime CSAI (Britannia Pharmaceuticals, Surrey, UK), but still suffering intractable nocturnal hypokinesia. Exclusion criteria were: 1) patients who were bedridden; 2) history of neurological disorders (except PD) or other muscle and joint diseases; and 3) a history of hypnotic or sedative drug use. The study was approved by the Human Ethics Committee of the Faculty of Medicine, Chulalongkorn University. All subjects gave informed consent before entering the study in accordance with the declaration of Helsinki.

Demographic and clinical characteristics were recorded including disease duration. Disease stage was rated using the Hoehn and Yahr (HY) staging system during the 'on' period. In order to accurately determine the severity of PD during the night, Unified Parkinson's Disease Rating Scale section 3 (UPDRS-3) was rated by JS at 2100 h in all subjects in their homes before and during nocturnal apomorphine infusion. The UPDRS axial score was calculated as the summation of items 18, 22, 27, 28, 29, and 30 of the UPDRS-3 [19]. As verified by sleep diaries, all subjects went to sleep after 2100 h. To quantify the severity of nocturnal symptoms, the Modified Parkinson's Disease Sleep Scale (PDSS-2) and the Nocturnal Akinesia Dystonia and Cramp Scale (NADCS) were recorded in all patients [1,20]. Overall dopaminergic treatment was quantified by calculating the levodopa equivalent dose (LED) in mg per day [21]. In addition, nocturnal dopaminergic treatment was estimated from the dopaminergic dose taken before going to bed and expressed in LED.

2.2. Selection of patients for nocturnal apomorphine infusion and experimental protocol

Patients were selected to undertake a semi-structured interview if they reported the symptoms of difficulty turning around or finding a comfortable sleep position consistent with impaired bed mobility during the past week [17]. To confirm the subjective complaints of impaired bed mobility, they must have reported the severity of at least 1 on item 9 of the PDSS-2 ('Did you feel uncomfortable at night because you were unable to turn around in bed or move due to immobility?') and a severity of at least 0.5 on the nocturnal akinesia sub-score of the NADCS [20,22]. The severity of both scales was evaluated by two independent neurologists (RB and JS) who were required to agree on their rating assessment. In case of the disagreement, both physicians assessed the evidence again, and arrived at a consensus. In order to fulfill the selection criteria for nocturnal apomorphine infusion, nocturnal hypokinesia had to be present as identified by both rating scales. In addition, the infusion dosage of daytime CSAI and all other dopaminergic medications must have been kept unchanged for at least one month prior to the addition of nocturnal infusion.

Before entering into the nocturnal infusion study, all subjects were given their daytime CSAI between 0800 h and 2000 h using the Crono Apo-Go III portable infusion pump (Genus Pharmaceuticals Ltd., Berkshire, UK) for ambulatory use connected to a subcutaneously inserted cannula. Due to a concern of possible tolerance, the Food and Drug Administration (FDA) of Thailand stipulates an overnight period without apomorphine treatment of at least four hours [23]. Therefore, in all subjects, the daytime CSAI was continued as a night-time infusion at the same infusion dosage until 0400 h the following day giving a total of a 20-h continuous infusion for a 24-h period (Fig. 1). All subjects had a 4-h period without infusion between 0400 h and 0800 h, before starting the next CSAI at 0800 h. The main reason that an infusion free period was chosen between 0400 h and 0800 h was because all subjects were stabilized with daytime CSAI prior to the enrollment of this study and we did not want to compromise patient's daytime symptoms by omitting infusion during the daytime. Moreover, it was practically difficult for subjects and caregivers to omit CSAI in the early evening and to restart CSAI again in the late hours of the night.

2.3. Wearable sensors

The inertial sensor (NIGHT-Recorder) used in this study was developed by our group with technical development and experimental verification described elsewhere [18]. In brief, the NIGHT-Recorder consists of a 16-bit digital-output triaxial integrated microelectromechanical system (iMEMS) accelerometer and gyroscope that are capable of measuring linear and angular accelerations in three translational planes (x,y,z). The recordings were

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