PRDOA 12 (2025) 100306

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.sciencedirect.com/journal/clinical-parkinsonism-and-related-disorders

Case Reports

Memantine-induced delayed sleep phase in Huntington's disease: A case report

Youshi Fujita [a,*], Toshio Hamada [b], Satoshi Kubota [a], Tomomi Sakoh-Goshima [a], Hirotaka Shirasaki [a]

[a] Fujita Neurological Hospital, 31-12-1 Hasaki, Maruoka, Fukui 910-0367, Japan
[b] Department of Neurology, Fukui Prefectural Hospital, 2-8-1, Yotsui, Fukui 910-8526, Japan

ARTICLE INFO

Keywords:
Memantine
Delayed sleep phase
Huntington's disease
Circadian rhythm
Actigraphy

ABSTRACT

Circadian rhythm sleep disorders may occur after memantine administration. We describe a 49-year-old woman with Huntington's disease, who complained of sleep onset insomnia following the administration of memantine. Memantine reduced hyperkinetic movements but led to delayed sleep phases, that were dose-dependent and reversible, confirmed by sleep logs and actigraphy.

Huntington's disease (HD) is a hereditary neurodegenerative disease characterized by movement disorders such as chorea and dystonia, along with psychiatric symptoms and cognitive decline. Other notable aspects of this disease include sleep disruption and circadian rhythm disturbance [1].

Memantine is a well-tolerated N-methyl-D-aspartate receptor antagonist used for the treatment of moderate-to-severe Alzheimer's disease. The most common adverse events at increased risk with memantine are dizziness and headache.

Here, we present a case of Huntington's disease in which memantine reduced involuntary hyperkinetic choreic movements but caused sleep-wake rhythm disturbances and delayed sleep phase, as confirmed by actigraphy.

A 49-year-old woman who had been diagnosed with HD 8 years previously visited our hospital concerned about worsening involuntary hyperkinetic choreic movements and declining cognitive function. During her 30 s, she had experienced behavioral and psychiatric symptoms, including irritability and abrupt outbursts of angry and violent behavior, and involuntary movements had becoming apparent. Magnetic resonance imaging revealed mild atrophy of the caudate and putamen, and genetic analysis revealed an extended CAG repeat (43 repeats) in the HD gene (IT15).

For the worsening hyperkinetic choreic movements and cognitive decline, memantine was initiated at 5 mg and increased by 5 mg every other week to reach 20 mg in 3 weeks. She had been taking haloperidol 2 mg, perospirone 4 mg, and thiapride 75 mg, and continued these medications. Before memantine administration, she had no difficulty falling asleep at about 11:30p.m. and slept uninterrupted for 7 to 8 h. She remained on memantine 20 mg for two weeks but reported difficulty falling asleep at night and waking up in the morning, although her hyperkinetic movements had decreased. The day after the dose was reduced from 20 mg to 10 mg, her difficulty falling asleep resolved, and her hyperkinetic choreic movements were less severe than before administration. The Mini-Mental State Examination score and total score of the motor assessment section of the Unified Huntington's Disease Rating Scale (maximum 124) before and 2 weeks after the reduction to memantine 10 mg were 23/30 and 20/30, and 50 and 46, respectively. Actigraphic recordings confirmed that both sleep onset and final awakening times with memantine 20 mg were delayed by 2 to 3 h compared to pre-treatment, with sleep onset between 12:00 am and 3:00 am and final awakening between 8:00 am and 10:00 am. The delayed sleep phase returned to pre-dose levels the day after the memantine dose was reduced from 20 mg to 10 mg (Fig. 1A). Activity counts with reference to physical movement over 24 h were reduced with 20 mg of memantine compared to the pre-dose period. Activity counts were higher with memantine at 10 mg than 20 mg but lower than those before administration. Conversely, activity counts during nighttime (11:30p.m. to 7:30 a.m.) were significantly increased with 20 mg but returned to pre-dose levels with 10 mg (Fig. 1B).

In this case of Huntington's disease, we found that memantine

* Corresponding author at: Fujita Neurological Hospital, Fukui 910-0367, Japan.
E-mail address: fujitauc@fuhp.or.jp (Y. Fujita).

https://doi.org/10.1016/j.prdoa.2025.100306
Received 7 November 2024; Received in revised form 25 January 2025; Accepted 16 February 2025
Available online 17 February 2025

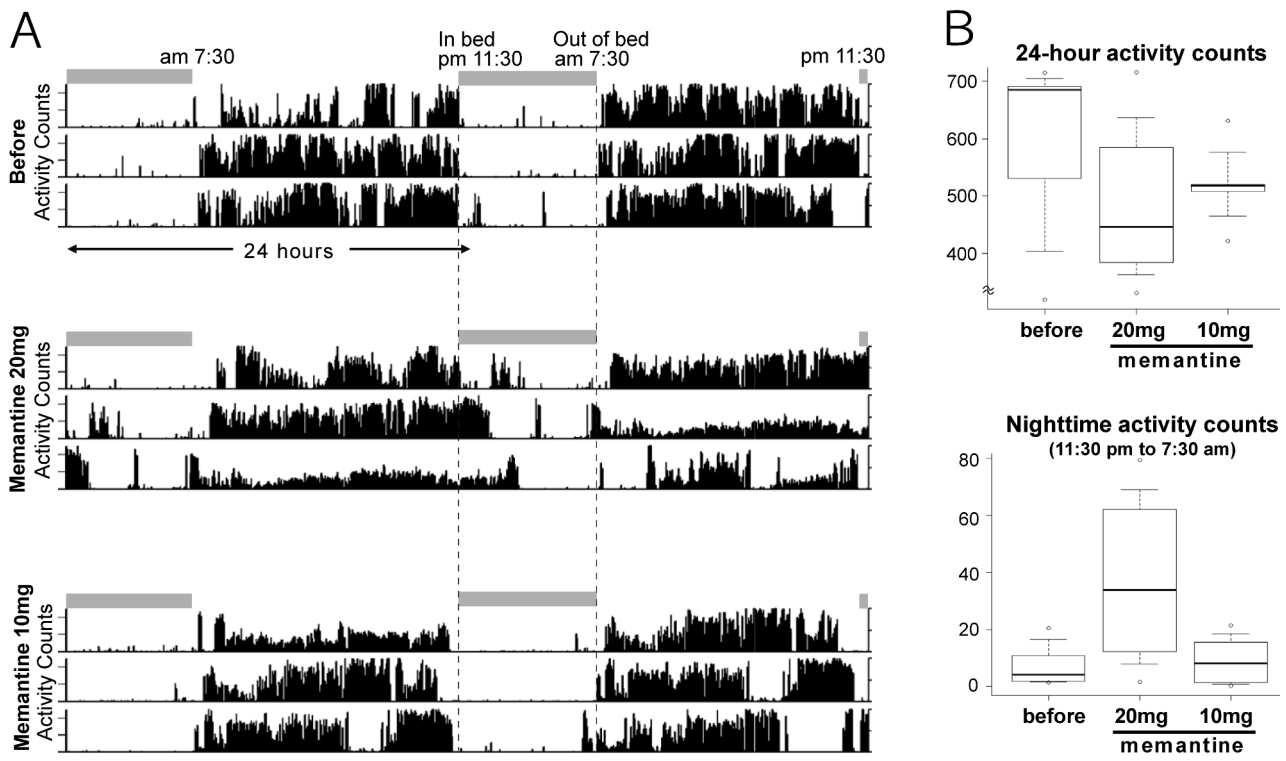

Fig. 1. A. Actigraph recordings. Actigraphic recordings sufficient for analysis were taken on five consecutive days before administration, four consecutive days at a memantine dose of 20 mg, and six consecutive days after the dose was reduced to 10 mg. The right half of each row is identical to and overlaps with the left half of the following row, showing that these are continuous records. Four consecutive days (three rows) from each period are shown. Gray bar lines represent the usual time in bed before memantine administration, with an in-bed time of 11:30 pm and an out-of-bed time of 7:30 am. B. Changes in physical activity and hyperkinetic movement. The activity count is a numerical value that reflects the intensity and frequency of movements. The boxes represent interquartile ranges, and the horizontal line in each box represents the median. The whiskers show the minimum and maximum values or values up to 1.5 times the interquartile range below or above the first or third quartile if outliers are present (circles). The 24-hour activity counts (mean ± SD) were 588.1 ± 167.1, 484.4 ± 163.4, and 519.7 ± 66.6 × 10^4 before, with 20 mg, and with 10 mg of memantine, respectively. Nighttime activity counts were 7.7 ± 8.0, 38.1 ± 31.8, and 9.1 ± 9.2 × 10^4, respectively. Nighttime activity counts significantly increased with 20 mg compared to pre-administration levels (P = 0.0441, one-way ANOVA with Dunnett's post hoc test).

reduced hyperkinetic movements but caused sleep-wake rhythm disturbances and sleep phase regression. Both the reduction in hyperkinetic movements and sleep phase regression were dose-dependent. In contrast, no improvement in cognitive function was observed. To our knowledge, memantine-induced delayed sleep phase episodes have not been previously reported.

Memantine is a non-competitive *N*-methyl-d-aspartate receptor antagonist used to treat moderate to severe Alzheimer's disease. Several reports with a limited number of patients have indicated that memantine reduces hyperkinetic movements and slows the progression of HD [2–4]. However, a more recent large-scale retrospective study found no clinical benefit in cognitive function or Total Functional Capacity scores, which reflect motor abilities not directly measure motor function [5], and thereby challenged the effectiveness of memantine treatment for HD. The inconsistencies in earlier findings on motor function might result from factors such as the memantine dosage, duration of administration, disease stage and severity, follow-up period, motor assessment methods, or concomitant medications.

The development of delayed sleep phase in our case might have been affected by both intrinsic and extrinsic factors. Huntington's disease is known to be accompanied by circadian rhythm disturbances and sleep phase regression, which are assumed to be caused by hypothalamic disturbances [1]. In a rodent model, memantine increased sleep latency and altered sleep-wake architecture in a dose-dependent manner [6,7]. A plausible mechanism for the sleep phase regression in our case may be that HD-related circadian rhythm disturbances were modified and amplified by the administration of memantine.

This case report indicates that memantine may reduce hyperkinetic movements in HD but also lead to sleep phase regression. Both the reduction in hyperkinetic movements and sleep phase regression were dose-dependent and reversible. Accordingly, the possibility remains that some HD patients would benefit from memantine by adjusting the dosage for hyperkinetic movements. Administration of memantine should be done with caution to avoid unnecessary pharmacological interventions for nighttime sleep onset insomnia, particularly for conditions such as HD that are susceptible to sleep phase regression.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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