Melatonin Receptor Agonists for Treating Delirium in Elderly Patients with Acute Stroke

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Background: Delirium is considered to worsen life prognosis in elderly patients with stroke. We examined the effects of the melatonin receptor agonist ramelteon for treating delirium in elderly stroke patients with insomnia in comparison to the other drugs. *Methods:* Elderly patients with delirium and insomnia after acute stroke who were treated with ramelteon (7 patients; mean age 76 years) and the other drugs (21 patients; mean age 77.3 years) between July 2011 and March 2012 at our hospital were retrospectively examined. *Results:* All patients treated with ramelteon had a significant improvement within a week and were started on early and aggressive rehabilitation. No patient experienced oversedation, neurologic deterioration, or any other worsening effect associated with ramelteon treatment. *Conclusions:* Melatonin receptor agonists may be effective for the treatment of delirium in elderly patients with acute stroke. **Key Words:** Acute stroke—delirium—elderly individuals.

Stroke is a recognized predisposing factor for the development of delirium.[1] Delirium is a severe disorder that is common among elderly hospital patients[2] and is associated with increased mortality, morbidity, and length of hospital stay.[3,4] Currently, there are no clear guidelines for the treatment of delirium in stroke patients.

We report 7 cases in which the melatonin receptor agonist ramelteon was clinically effective for treating delirium in patients >65 years of age who had been hospitalized with acute stroke and insomnia.

Methods

A total of 368 patients with acute stroke (72 ± 12.1 years of age; 201 males and 167 females; 249 patients with cerebral infarction, 93 patients with cerebral hemorrhage, and 26 patients with subarachnoid hemorrhage) were treated in our hospital between July 2011 and May 2012. Patients in this group ≥65 years of age with associated insomnia and delirium who were treated with ramelteon and/or the other sedatives or antipsychotic drugs within 3 weeks of admission were reviewed retrospectively in this study, which examined the effectiveness and adverse effects of ramelteon. We regularly performed the diagnosis of delirium based upon the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[5] and evaluated the degree of delirium according to the Richmond Agitation and Sedation Scale (RASS)[6] (Table 1). We first assessed the diagnosis of delirium by CAM-ICU; the medication was chosen by each doctor. RASS was scored immediately before and 1 week after administration of the medication. National Institutes of Health Stroke Scale (NIHSS) scores were evaluated on admission (pre-NIHSS) and on day 30 (post-NIHSS).

Differences in the clinical, demographic, and cognitive variables between the ramelteon arm and the other were examined when available using the Student t (for continuous data) and the Fisher exact tests (for categorical data). Two-tailed P values $< .05$ were considered statistically significant.

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Results

Thirty-five patients (9.51%) had insomnia and delirium. Twenty-nine of them (82.9%) were ≥65 years of age. One patient who was treated simultaneously with ramelteon and brotizolam was excluded. Seven patients (76 ± 6.5 years of age; 4 males and 3 females; 5 patients with cerebral infarction, 1 with cerebral hemorrhage, and 1 with subarachnoid hemorrhage) were treated with ramelteon (Table 2), and 21 patients (77.3 ± 5.53 years of age; 11 males and 10 females; 13 patients with cerebral infarction, 7 with cerebral hemorrhage, and 1 with subarachnoid hemorrhage) were treated with other drugs, such as brotizolam, zopiclone, and haloperidol. Age, sex, type of stroke, pre- and post-NIHSS scores, the timing of administration of the medication, and pre-RASS score were not significantly different in both treatment arms. By contrast, the patients who had at least 1 of 3 of the following symptoms—aphasia, neglect, or visual disturbance, which are established risk factors for delirium[1]—were significantly more ($P = .029$) and difference in pre-/post-NIHSS score and post-RASS score were significantly better ($P = .011$ and .013) in the ramelteon arm (Table 3).

In the ramelteon arm, all of the patients had some beneficial effect within 7 days at the latest, including 3 patients with marked improvement in the RASS score on the day after administration and 1 patient on the third day. Sleep induction was effective and rapid in all patients. Neurologic deterioration, oversedation, or significant changes in laboratory tests did not occur in any patient. Delirium was well controlled by ramelteon in a continuous manner even in the chronic phase, which led to smooth initiation of aggressive rehabilitation. One patient was excluded from the analysis because he was treated simultaneously with ramelteon and brotizolam. Even in that case delirium was well controlled by the addition of ramelteon after the ineffective treatment by brotizolam. Two representative cases are described below.

Case 1

Case 1 was a 76-year-old man with the chief complaint of right hemiparesis. His medical history included hypertension, atrial fibrillation, and chronic pulmonary obstructive disease. The patient was found lying on the floor and transferred to our hospital. He had a mild disturbance of consciousness, right hemiplegia, right facial palsy, aphasia, visual disturbance, and neglect to the right side (NIHSS score 24 points). A magnetic resonance imaging scan of his head revealed an occlusion of the left middle cerebral artery distal to the M2 segment and a large acute cerebral infarction involving the left caudate head and temporal/parietal/frontal lobes. Although continuous heparin infusion for a suspected cardiogenic brain embolism was initiated, he often removed his urinary catheter and intravenous cannula and rejected rehabilitation. At night, he shouted and behaved violently toward the medical staff without sleeping (RASS +4).

Ramelteon was administered orally at a dose of 8 mg at 10 PM on day 8 in the hospital. He fell asleep some hours later and woke up at 9 AM the next day. He never became violent to the staff afterward and slept well at night with continuing ramelteon therapy. He became eager to undergo rehabilitation and was able to communicate by gesturing and remain in the sitting position in a wheelchair with a NIHSS score of 12 points.

Case 6

Case 6 was a 71-year-old man with the chief complaint of unsuccessful communication. His medical history included hypertension. The patient was admitted to our hospital with symptoms of vomiting and aphasia (pre-NIHSS score 7 points). A computed tomographic scan of his head revealed a small left frontal subcortical hemorrhage. Conservative treatment including control of blood pressure was administered. He showed restlessness just after hospitalization and removed intravenous cannula and against our advice began walking during nighttime (+3 RASS).

Ramelteon was administered orally at a dose of 8 mg at 10 PM on the first day. Although he woke up at midnight and removed his catheter during daytime for 5 consecutive days, he slept well on day 6 and became eager to undergo rehabilitation. He was able to speak fluently and understand clearly on day 30 (post-NIHSS score 0 points).

Table 1. *The Richmond Agitation Sedation Scale*

Score	Term	Description
+4	Combative	Overtly combative, violent; immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement; fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 sec)
−2	Light sedation	Briefly awakens with eye contact to voice (<10 sec)
−3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
−5	Unarousable	No response to voice or physical stimulation