Off-Label Drug Uses

Delirium: Ramelton

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@kumc.edu.

BACKGROUND

Delirium is a common complication associated with hospitalization, particularly in those receiving care in an intensive care unit (ICU) or postoperative setting. In elderly inpatients, delirium has been associated with increased morbidity, mortality, and length of stay.¹ Antipsychotics (eg, haloperidol) typically used to treat agitation associated with delirium may carry the risks of oversedation and QT prolongation. Although the exact cause of delirium has not been clearly established and is considered multifactorial, recent evidence has suggested that in some cases disturbances in sleep-wake cycles and melatonin levels may play a role in the development of delirium. Ramelton, a hypnotic, has significant activity at melatonin-1 and -2 receptors and thus has been proposed as a treatment for delirium.

PATIENT POPULATION

Adult inpatients with delirium due to various causes.

DOSAGE AND DURATION

Oral ramelton has been administered as 8 mg nightly at bedtime for up to several weeks.

RESULTS

Oral ramelton in the management of delirium in adult inpatients has been studied in case report data and noncontrolled settings in fewer than 20 patients with favorable results.^{2–4} Variances in methodology

and patient populations limit the validity of these results. Current clinical practice guidelines for the management of pain, agitation, and delirium in adult ICU patients do not mention ramelton.¹

Guidelines

American College of Critical Care Medicine (ACCM), Society of Critical Care Medicine (SCCM), and American Society of Health-System Pharmacists (ASHP)

The current ACCM, SCCM, and ASHP clinical practice guidelines for the management of pain, agitation, and delirium in adult ICU patients recommend early mobilization of the patients to reduce the incidence and duration of delirium (level of evidence +1B). In the prevention of delirium, the guidelines provide no recommendation for using a pharmacologic delirium prevention protocol or a combined nonpharmacologic/pharmacologic delirium prevention protocol in adult ICU patients based on a lack of data (0,C). In addition, these guidelines do not suggest the use of haloperidol or atypical antipsychotics (-2C) and provide no recommendation for the use of dexmedetomidine in the prevention of delirium in the ICU patients.

For the treatment of delirium, the guidelines state that there is no evidence to support the use of haloperidol in the reduction of duration of delirium in adult ICU inpatients. However, the use of atypical antipsychotics may reduce the duration of delirium (C), but these guidelines also state that antipsychotics should not be used in patients at significant risk for torsades de pointes (-2C). Rivastigmine is not

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recommended (-1B). In adult ICU patients with delirium unrelated to alcohol/benzodiazepine withdrawal, continuous infusions of dexmedetomidine are recommended over benzodiazepine infusions for sedation to reduce the duration of delirium (+2B).

In addition, several nonpharmacologic measures, including promoting sleep, are recommended as strategies in the management of pain, agitation, and delirium to improve ICU outcomes.

Ramelton is not mentioned in these guidelines.¹

Noncontrolled Trials

In a retrospective review, 368 inpatients with acute stroke (mean age 72 years) were treated between July 2011 and May 2012. Of these, 29 patients were at least 65 years of age with insomnia and delirium and received either ramelton (n=7; mean age 76 years) or other therapy (sedatives, antipsychotics; n=21; mean age 77.3 years) within 3 weeks of admission. One patient, receiving combination therapy with ramelton, was excluded. Delirium was diagnosed via the Confusion Assessment Method for the ICU (CAM-ICU) and assessed for degree of severity via the Richmond Agitation and Sedation Scale (RASS). In the ramelton arm, all of the patients had some clinical improvement within 1 day at the earliest and within 7 days at the latest. Mean RASS scores showed reduction at 1 week post therapy when compared to baseline values (2.71 vs 0.29). In the other arm, mean RASS scores were reduced from 2.57 to 1, respectively. The difference in the pre/post National Institutes of Health Stroke Scale (NIHSS) and RASS scores were significantly better in the ramelton arm when compared to the other therapy arm. The authors concluded that ramelton may be a beneficial treatment of delirium associated with stroke in the elderly.²

Case Reports

Three female inpatients (age range, 59 to 83 years) meeting diagnostic criteria for delirium and exhibiting symptoms of disorientation, restlessness, and sleep disturbances were administered oral ramelton (8 mg nightly) at 9:00 p.m. Concurrent antipsychotic therapy was not administered. Baseline values of the Memorial Delirium Assessment Scale (MDAS) ranged from 14 to 24. Within 7 days of ramelton therapy, the MDAS scores significantly improved in all patients (range, 4 to 7). Based on these limited data, the authors suggested that ramelton may be of benefit in the management of delirium.³

Five patients with delirium due to varying causes (eg, Alzheimer dementia, steroid psychoses, dementia with Lewy bodies) were treated with oral ramelton (8 mg) at bedtime to modify the sleep-wake cycle. Four patients were unresponsive to previous therapy with various medications, commonly including antipsychotics. Baseline Delirium Rating Scale (DRS) scores ranged from 18 to 24 (maximum 39). In all 5 cases, recovery from delirium occurred within 24 hours with DRS scores decreasing (range, 5 to 24). Improvements in symptoms were not limited to corrections in the sleep-wake cycle, but also included improved attention and cognitive function. The authors concluded that this agent may be a viable agent in the management of delirium.⁴

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, warnings/precautions, adverse reactions, drug interactions).

Adverse events related to ramelton were not observed in the reviewed data.

THERAPY CONSIDERATIONS

Current evidence from a small number of inpatients in noncontrolled settings regarding the use of ramelton in the management of delirium due to various causes suggests a beneficial effect in reversing symptoms. Clinical practice guidelines for the management of pain, agitation, and delirium in ICU adult patients does not mention this agent. Larger controlled trials are needed before this agent's role in the therapy of delirium is established.

REFERENCES

1. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013; 41:263-306.
2. Ohta T, Murao K, Miyake K, Takemoto K. Melatonin receptor agonists for treating delirium in elderly patients with acute stroke. *J Stroke Cerebrovasc Dis*. In press.
3. Kimura R, Mori K, Kumazaki H, Yanagida M, Taguchi S, Matsunaga H. Treatment of delirium with ramelton: initial experience in three patients. *Gen Hosp Psychiatry*. 2011;33: 407-409.
4. Furuya M, Miyaoka T, Yasuda H, et al. Marked improvement in delirium with ramelton: five case reports. *Psychogeriatrics*. 2012;12:259-262. ■