Off-Label Drug Uses

Melatonin: Delirium (Postsurgical)

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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 in a postoperative setting. In elderly inpatients, delirium has been associated with increased morbidity, mortality, and length of stay.¹ A review of postoperative studies has suggested that decreased melatonin levels in the postoperative period may be associated with an increased risk of delirium.^{2,3} Though 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. Thus, melatonin has been proposed as a preventive measure or treatment for delirium in postoperative patients.

PATIENT POPULATION

Elderly inpatients (at least 65 years old) undergoing surgery.

DOSAGE AND DURATION

Oral melatonin has been administered as 5 mg at sleep on the night of operation and 5 mg 90 minutes preoperatively. In patients who appear to develop postoperative delirium, melatonin 5 mg was also administered at night on postoperative days 1 through 3.⁴

RESULTS

Oral melatonin in the management of delirium in adult inpatients undergoing surgery has been reported

in a limited number of controlled trials enrolling approximately 300 patients and demonstrating favorable results in the prevention of delirium when compared to placebo, midazolam, and clonidine. This agent may have some utility in treatment once postoperative delirium has developed.⁴ Current clinical practice guidelines for the management of pain, agitation, and delirium in adult ICU patients do not mention the use of melatonin.¹

Guidelines

The current American College of Critical Care Medicine (ACCM), Society of Critical Care Medicine (SCCM), and American Society of Health-System Pharmacists (ASHP) clinical practice guidelines for the management of pain, agitation, and delirium in adult ICU patients recommend early mobilization of the patient to reduce the incidence and duration of delirium (level +1B evidence). 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

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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 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 for strategies in the management of pain, agitation, and delirium to improve ICU outcomes.

Melatonin is not mentioned in these guidelines.¹

Controlled Trials

In a double-blinded trial, 300 patients at least 65 years of age who were scheduled for hip arthroplasty and receiving spinal anesthesia were randomized to 1 of 4 groups to receive a premedication regimen: (1) control (receiving no premedication); (2) oral melatonin (5 mg); (3) oral midazolam (7.5 mg); and (4) oral clonidine (100 mcg). The medications were administered orally at sleep time on the night of the operation and 90 minutes preoperatively. Of the 300 patients, 78 were determined to already have delirium via the Abbreviated Mental Test (AMT score <8) and an additional 19 patients were excluded for various reasons (eg, receiving general anesthesia or postoperative ICU admission). A total of 203 patients completed the study. Patients with AMT scores less than 8 on the day of the operation and the following 3 postoperative days were considered to have developed postoperative delirium. These patients received melatonin (5 mg daily for 3 days) and were reassessed each day for 3 days. After the third postoperative day, the total percentage of patients with delirium was significantly higher in the midazolam (44%), clonidine (37.25%), and control groups (32.65%) when compared to the melatonin group (9.43%) ($P < .05$).

Of the 62 patients who received melatonin postoperatively, 58.06% ($n = 36$) did not develop delirium. The authors concluded that only melatonin significantly reduced the incidence of postoperative delirium to 9.43% ($P = .003$).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 melatonin were not observed in the reviewed data.

THERAPY CONSIDERATIONS

Current evidence from a limited number of controlled trials regarding the use of melatonin in the management of postoperative delirium suggests a beneficial effect in preventing symptoms and may have some utility in treatment once delirium has occurred. Clinical practice guidelines for the management of pain, agitation, and delirium in the ICU adult patients do not mention this agent. Larger controlled trials are needed before this agent's role in the management of delirium is established.

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