MELATONIN FOR ICU DELIRIUM: IN SEARCH OF A SILVER BULLET

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Pharmacist Objectives

- Discuss current guideline recommendations for the prevention and treatment of delirium in the intensive care unit (ICU).

- Determine the role of melatonin supplementation for the prevention and treatment of delirium in critically ill patients.

Technician Objective

- Explain melatonin doses and indications for use in inpatient practice

Disclosure Statement

- No relevant financial or commercial relationships to disclose

2013 Pain, Agitation, and Delirium (PAD) Guidelines

- Routinely assess pain, agitation, and delirium
- Utilize an *analgesia-first* sedation strategy using intravenous opioids
- Target light levels of sedation using non-benzodiazepine sedatives only after pain is controlled and/or perform daily awakenings
- Implement delirium prevention strategies
- Consider pharmacologic delirium treatment

Crit Care Med. 2013;41(1):263-306.

ICU Delirium

- Cardinal features
  - Disturbed level of consciousness with reduced ability to focus, sustain, or shift attention
  - Either a change in cognition or development of a perceptual disturbance
- Pathogenesis remains unclear
- Independent predictor of negative clinical outcomes, including long-term cognitive dysfunction

Crit Care Med. 2013;41(1):263-306.
Crit Care Med. 2016;44(1):207-17.

PAD Guidelines: Delirium Prevention

- Avoid benzodiazepines in most patients
- Early mobilization
- Frequent orientation to person, place, and time
- Protection of sleep-wake cycles
- Pharmacologic prophylaxis provides no benefit

Crit Care Med. 2013;41(1):263-306.

PAD Guidelines: Delirium Treatment

- Atypical antipsychotics may reduce delirium duration
- There is no published evidence that treatment with haloperidol reduces the duration of ICU delirium
- Dexmedetomidine recommended for sedation over benzodiazepines to decrease delirium duration

Crit Care Med. 2013;41(1):263-306.

Circadian Rhythm and ICU Delirium

- Sleep-wake cycles are reliably disrupted in critical illness
- Circadian dysrhythmias and delirium appear to be intricately related
- Chronotherapy aims to reset abnormal circadian rhythms
  - Morning exposure to bright light
  - Concentrated nighttime dark periods
  - Melatonin supplementation or agonism

Crit Care. 2009;13(6):234-41.
Crit Care Med. 2016;44(1):207-17.

Melatonin for Delirium Prevention

Study	Intervention	Implications
Sultan SS. Saudi J Anaesth. 2010; 4(3):169-73.	Melatonin 5 mg, midazolam 7.5 mg, or clonidine 0.1 mg for 2 doses	• Decreased delirium in the melatonin group • Extensive exclusion criteria • Dosed the night prior to the scheduled operation and 90 minutes preoperatively
Al-Aama T, et al. Int J Geriatr Psychiatry. 2011; 26(7):687-94.	Melatonin 0.5 mg nightly for up to 14 days	• Decreased delirium in the melatonin group • No differences between groups in sleep outcomes • Elderly patients on a general medical ward
de Jonghe A, et al. CMAJ	Melatonin 3	• Similar incidence of delirium between groups

Melatonin for Sleep in the Critically Ill

Study	Intervention	Implications
Shilo, et al. Chronobiol Int. 2000;17(1):71-6.	Melatonin SR 3 mg for 2 nights	• Stable hemodynamics required • Increased total sleep time with melatonin • No assessment of delirium
Ibrahim, et al. Crit Care Resusc. 2006; 8(3):187-91.	Melatonin 3 mg for ≥2 nights	• Similar duration nocturnal and diurnal sleep • Increased agitation in the melatonin group • Sleep duration and quality assessed by bedside nurse
Bourne, et al. Crit Care. 2008;12(2): R52-60	Melatonin 10 mg for 4 nights	• Nocturnal sleep time increased one hour with melatonin • Deeper sleep with melatonin as measured by BIS

Ramelteon for Delirium Prevention

- Effect of ramelteon 8 mg versus placebo on the incidence of delirium
- Delirium occurred in 3% of the ramelteon group versus 32% of the placebo group (p = 0.003)
- No difference in sleep-related outcomes
- Limitations
  - Strict exclusion criteria, including patients requiring intubation
  - Low severity of illness
  - Japanese population
  - Different appearance of ramelteon and placebo

JAMA Psychiatry. 2014;71(4):397-

Conclusions

- No robust or high quality evidence to suggest melatonin or melatonin agonists affect ICU delirium
- The mainstay of delirium prevention is early progressive mobility
- It is reasonable to employ additional nonpharmacological interventions to control environmental stimuli and preserve circadian rhythms

Self-Assessment Question

KG is a 68 YOF admitted with severe sepsis due to pneumonia. She was intubated upon admission and has been transferred to the ICU. She has no pertinent PMH or social history. Which is the best option to implement for delirium prevention in this patient?

A. Quetiapine 25 mg via NG tube three times daily
B. Progressive mobility protocol beginning today
C. Melatonin 3 mg via NG tube at bedtime
D. Lorazepam IV infusion titrated to attain a deep level of sedation