

Iatrogenic opioid withdrawal syndrome presentation and considerations

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ABSTRACT

The 2018 Critical Care Medicine Guidelines for Analgesia and Sedation in the ICU Good Practice Statement emphasized the importance in the treatment of pain taking precedence over sedation. Within these guidelines, a multimodal analgesia approach is standard of care in the ICU, which often includes the initiation of opioids. As practice has shifted to prioritize pain management over sedation, opioids have been administered in frequent and prolonged dosages, making the critically ill patient susceptible to iatrogenic opioid withdrawal syndrome (IOWS). This article provides an overview of IOWS to alert clinicians to the diagnosis of IOWS in ICU patients.

Keywords: opioids, withdrawal, ICU, mechanical ventilation

OBJECTIVES

1. Describe a case of likely iatrogenic opioid withdrawal syndrome
2. Describe the epidemiology of IOWS
3. Discuss possible differential diagnoses when considering IOWS
4. Review the diagnostic criteria, evaluation, and treatment of IOWS
5. Summarize the importance of interdisciplinary collaboration in detecting IOWS in the intensive care setting

INTRODUCTION

The 2018 Critical Care Medicine Guidelines for Analgesia and Sedation in the ICU Good Practice Statement emphasized the importance in the treatment

of pain taking precedence over sedation. Within these guidelines, a multimodal analgesia approach is standard of care in the ICU, which often includes the initiation of opioids.¹ As practice has shifted to prioritize pain management over sedation, opioids have been administered in frequent and prolonged dosages, making the critically ill patient susceptible to iatrogenic opioid withdrawal syndrome (IOWS). Studies suggest that over 80% of mechanically ventilated adults are managed with opioids.² However, there is limited knowledge on the incidence and management of iatrogenic opioid withdrawal syndrome in critically ill patients. This article provides an overview of IOWS in these patients.

CASE STUDY

A 41-year-old man developed acute hypoxemic respiratory failure secondary to COVID-19 pneumonia and required intubation and mechanical ventilation for a prolonged period. Due to the patient's body habitus (BMI 42.8 kg/m²) and poor response to sedation, he required high dose pain management with fentanyl over 2 weeks. He received approximately 50,000 mcg of fentanyl IV and other sedatives for agitation over

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17 days. These other sedatives included intermittent use of propofol, dexmedetomidine, ketamine, midazolam, clonazepam, quetiapine, and methadone. Throughout this period, he had frequent episodes of hypertension, delirium, agitation, and combativeness, especially during periods of dose reduction. Post-extubation, he received fentanyl at 10 micrograms per hour for three days to limit withdrawal symptoms and was weaned off all sedation on hospital day 17. At this point, he was alert and oriented and did not have any signs of opioid withdrawal. The patient was discharged home after a 22-day hospitalization without an opioid prescription.

What was the cause of this patient's agitation during the reduction of his opioid dose during the weaning and extubation phase of his hospitalization? Important considerations include encephalopathy related to viral infection, delirium related to acute respiratory failure and mechanical ventilation, direct drug toxicity secondary to drugs used during his complex clinical care, alcohol or substance withdrawal, and opioid withdrawal syndrome.

EPIDEMIOLOGY

There are limited data in adult patients on iatrogenic opioid withdrawal syndrome and no standard assessment tools. Prospective studies have shown that 16.7% to 55% of adults receiving opioids and/or benzodiazepines for 72 hours or more develop iatrogenic withdrawal in the ICU. Risk factors include higher total doses and prolonged administration of opioids and benzodiazepines.³ These patients often have acute medical disorders with significant comorbidity associated with pain and stress and may require multiple medications with central nervous system effects. This syndrome can develop in patients in medical ICUs, trauma ICUs, surgical ICUs, and burn ICUs. While more data are needed to determine the true incidence rate of iatrogenic opioid withdrawal in the ICU, particularly without confounding medications such as benzodiazepines, these prior studies indicate that recognizing the presentation and understanding management of opioid withdrawal are essential in the ICU.

DIFFERENTIAL DIAGNOSIS

1. Delirium

Delirium is an acute decline in cognition that fluctuates over hours to days and can present with hypoactivity or hyperactivity.⁴ Delirium is a clinical diagnosis that has several etiologies, including encephalopathy, infection, sepsis, metabolic abnormalities, drugs, endocrinopathies, cerebrovascular disorders, autoimmune disorders, seizure related disorders, neoplastic disorders, and hospitalization in general.⁴

2. Encephalopathy

Encephalopathy should be on the differential for IOWS. This can be associated with the primary diagnoses, such as sepsis, acute renal failure, and surgical procedures requiring anesthesia. Evaluation should include an electrolyte panel, liver function tests, and renal function tests.⁴

3. Drug and substance withdrawal—alcohol and benzodiazepines

Substance withdrawal from various drugs, such as benzodiazepines and alcohol, can cause features similar to IOWS. History should also consider prescription medications, such as anticholinergics, narcotics, or benzodiazepines and recreational drugs, such as alcohol, ecstasy, LSD, GHB, PCP, ketamine, cocaine, “bath salts,” and marijuana.⁴ Urine drug screens and blood alcohol levels could help make this diagnosis.

4. Drug toxicity

Medications, particularly those with anticholinergic effects and benzodiazepines, can cause delirium. Other toxins include inhalants, carbon monoxide, ethylene glycol, and pesticides.⁴

5. Iatrogenic opioid withdrawal syndrome

DIAGNOSTIC CRITERIA

The diagnosis of IOWS in critically ill adults with complicated medical care in ICUs represents a difficult problem. Other medical problems can lead to changes in the central nervous system and autonomic

nervous system which might be confused with iatrogenic opioid withdrawal. Alternative explanations for the development of these symptoms include direct drug toxicity, the development of pain and anxiety, and the development of delirium, encephalopathy, or withdrawal from additional substances.

The applicability of frequently used opioid withdrawal assessment tools for adult patients in the ICU is limited. Assessment tools, such as Subjective Opiate Withdrawal Scale and COWS, have been used only in the outpatient setting.⁵ While no specific patient population or setting is specified for the DSM-V opioid withdrawal criteria, using it in intensive care units could prove to be difficult and unreliable due to patients often being sedated, intubated, and unable to verbalize the presence of these symptoms.⁵

Classical diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders–5 (DSM-V) include a decrease or discontinuation in opioids or the administration of an opioid receptor antagonist, and three or more of the following: dysphoric mood, nausea, vomiting, muscle aches, lacrimation, rhinorrhea, pupillary dilation, piloerection, sweating, diarrhea, yawning, fever, and insomnia.⁶ In a prospective study assessing the DSM-V criteria in ICU IOWS, Taesotikul found the most common withdrawal symptoms were mydriasis (9/13), agitation (5/13), insomnia (5/13), and muscle pain (5/13). In addition, patients in the withdrawal group had a daily weaning rate of fentanyl greater than 50 mcg/hour.⁷

EVALUATION

Evaluation of a patient with possible IOWS should begin with a thorough history and physical examination. History should include medication history and duration, particularly opioids. Symptoms can include myalgias, hyperalgesia, gastrointestinal distress, anxiety or moodiness, dysphoria, irritability, insomnia, hot or cold flashes, or poor concentration.⁸ Key physical examination features may include autonomic instability, diaphoresis, rhinorrhea, yawning, increased lacrimation, muscle twitching, restlessness, vomiting, diarrhea, piloerections, tremors, mydriasis, cognitive impairment, and agitation.⁸

TREATMENT/MANAGEMENT

The approach to management should start with prevention by limiting the number of infused opioids to the extent possible and avoiding combinations with sedatives when possible. Should IOWS develop, treatment approaches include reinstating an opioid infusion with a slower rate of reduction and use of an alpha-2 agonist, such as dexmedetomidine or clonidine.^{5–9} The IOWS can significantly complicate the care of these patients and prolong mechanical ventilation and hospital length of stay. In addition, it is possible that patients with this syndrome are more likely to leave the hospital on opioids and require chronic opioid medications.¹⁰

ENHANCING HEALTHCARE TEAM OUTCOMES

IOWS is a condition that requires multiple medical disciplines to diagnose and treat. Using a team-based approach with scoring systems, titration of sedation and pain medications, and vigilance for IOWS can reduce the incidence of IOWS.

REVIEW QUESTIONS

1. A 46-year-old man requires mechanical ventilation for airway protection following the development of several generalized seizures. He has no prior history of a seizure disorder. No additional history is available from his family at this time. The most likely consideration is:
 - A. A new onset seizure disorder
 - B. Alcohol withdrawal syndrome
 - C. Recreational drug toxicity
 - D. Recent CNS trauma
2. This patient becomes agitated and requires an opioid infusion. Chest x-ray on the second day of hospitalization reveals an infiltrate at the right base consistent with aspiration. His gas exchange deteriorates and he requires mechanical ventilation for 5 days. During a spontaneous breathing trial, he becomes agitated. What are the possible considerations?

- A. Pain related to the use of an endotracheal tube
 - B. Alcohol withdrawal syndrome secondary to chronic alcohol use
 - C. Iatrogenic opioid withdrawal syndrome
 - D. Undiagnosed viral encephalitis which caused his initial presentation
3. What is the next step in his management?
- A. Restart opioid infusion
 - B. Consider using an alternative drug for sedation, such as clonidine.
 - C. Focus medical care nondrug management strategies, such as frequent orientation, establishing a normal sleep-wake schedule, and increasing mobility
 - D. Start a non-opioid sedative medication and use a standardized scale to adjust doses.

QUESTION ANALYSIS

It is not uncommon for patients to present to emergency department with altered levels of consciousness which may be associated with a seizure disorder. These patients are often intubated because the clinical course is uncertain and they are at risk for deterioration in respiratory status and aspiration. All the possible answers in question 1 represent reasonable choices. Past medical history, if available, may help establish the diagnosis. These patients will need careful physical examination looking for neurologic deficits, routine laboratory studies, alcohol levels, and drug toxicity screens. Computed tomography of the head may be necessary.

In general, patient is on mechanical ventilator should have a spontaneous awakening trial and spontaneous breathing trial every day in the morning. This provides an opportunity to evaluate their neurologic status and the respiratory status. It is not uncommon for patients to become agitated during this trial. This may be explained by pain and anxiety, drug or alcohol withdrawal, and the underlying initial diagnosis which may be associated with encephalopathy. Patient needs careful review at that time and likely needs reinstitution of drugs to maintain safety.

Management of patients on ventilators should focus on pain management and comfort. When possible, opioids and sedatives should slowly be tapered. Patients need frequent orientation, early mobility, and attention to sleep-wake schedules. Alternative medications, such as dexmedetomidine and clonidine, may provide adequate sedation and substitute for opioids.

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