Ethical Issues in Palliative Care
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Opioids, Iatrogenic Harm and Disclosure of Medical Error

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Abstract
The safety of patients in U.S. hospitals is a serious problem, with adverse events because of medical error affecting a significant proportion of hospitalized patients. Patients at the end of life are particularly vulnerable and are at risk of potential adverse events. This article presents a case in which opioids were rapidly titrated to neurotoxic doses in a patient who was terminally extubated. The patient was profoundly sedated and was noted to have Cheyne-Stokes breathing. The possibility of opioid-related iatrogenic harm is raised, and a discussion of what counts as medical error in these circumstances is explored. Palliative care specialists have a unique responsibility to provide guidance and establish a standard of care that clinicians should adhere to. Prevention of harm in dying patients should be a priority in the hospital setting. J Pain Symptom Manage 2010;39:309–313. © *2010 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

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Opioids, adverse events, medical error, palliative care

Introduction

Adverse events and medical error are unfortunately common occurrences in U.S. hospitals, affecting approximately 10% of hospitalized patients and causing hundreds of thousands of preventable deaths each year.[1] Serious adverse events in patients who have decided to focus on comfort and withdraw or withhold life-sustaining therapies have not been adequately studied. One source of potential harm in these patients may be the inappropriate escalation of opioid infusions for pain and dyspnea at the end of life.

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Opioid infusions are routinely started in the setting of terminal extubation to treat air hunger or when the goals of care shift to focus on comfort. It is not uncommon to observe clinicians in various settings, from the intensive care unit to neurology wards, prescribing opioids for patients at the end of life. Rapid titration of opioids or high-dose infusions may lead to serious adverse events, including sedation, myoclonus, seizures, and respiratory depression. Palliative care clinicians are in a unique position to help prevent opioid-related adverse events by providing education, guidance, and establishing a standard of care for such practices.

Case

JR was a 61-year-old married man with a past medical history significant for ST-elevation

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myocardial infarction (STEMI) complicated by cardiogenic shock, who underwent urgent coronary artery bypass grafting and repair of a ventricular septal defect. The postoperative course was complicated by admission to the coronary care unit in cardiogenic shock after suffering another myocardial infarction with atrial fibrillation and rapid ventricular response. He underwent cardioversion, emergent percutaneous coronary stenting, and placement of an intra-aortic balloon pump. Attempts at extubation were unsuccessful, and a tracheostomy was performed. He also developed multiple small parietal strokes of unclear etiology. During his stay in the unit, he could not be weaned off of pressors. His most recent echocardiogram revealed an ejection fraction of 12%, consistent with end-stage heart failure.

The patient was originally from the Dominican Republic. He was married and had six children and two ex-wives. He had been with his current wife for seven years. He was formerly a farm laborer. He had never been seriously ill before these recent episodes and, according to his son, had never taken "even an aspirin."

An ethics consultation was requested to help the family with establishing goals of care. The patient was unable to participate in decision making because of multifactorial encephalopathy. Both the patient's designated health care agent and the medical team agreed that aggressive resuscitation would offer little benefit, and the code status was changed to do not resuscitate. In addition, because the patient had mentioned to his son in the past that he would not want to be maintained artificially if there was no hope for meaningful recovery, the decision was made to focus exclusively on comfort care. The team explained that this meant stopping pressors and ventilatory support but continuing oxygen therapy through the tracheostomy collar and providing opioids if the patient experienced any respiratory distress or pain.

After extubation, the patient exhibited respiratory distress, which was managed with both morphine and hydromorphone. Lorazepam and haloperidol were used as needed for agitation; he remained deeply sedated. He was noted to have Cheyne-Stokes breathing, with apneic episodes lasting up to 20 seconds, followed by crescendo-decrescendo hyperventilation. This breathing pattern did not respond to increasing doses of opioids. Within a 24-hour period, his opioid infusions were rapidly titrated up to 50 mg/hour of morphine and 65 mg/hour of hydromorphone. No signs of myoclonus or seizures were noted.

The patient was transferred to a medicine floor, where he appeared to be hemodynamically stable off of pressor support. The ethics consultant expressed concern over the patient's opioid regimen and asked whether the Cheyne-Stokes respirations may have actually been a result of the opioids.

The Palliative Care Service was consulted to help provide intensive comfort measures and to evaluate the potential harm of high-dose opioids.

Ethical Analysis

The first issue to clarify is whether the patient's breathing pattern was the result of opioid boluses and infusions administered in the coronary care unit. Several studies have reported an association with opioids and abnormal breathing patterns, most notably central sleep apnea and ataxic breathing.[2–5] Biot's respiration, an abnormal pattern of breathing characterized by clusters of quick, shallow inspirations followed by periods of apnea, has also been observed in patients after opioid exposure.[6] Opioids are believed to lessen the sensitivity of the respiratory center to CO_2,[7] which may cause respiratory depression and Cheyne-Stokes breathing. Cheyne-Stokes breathing can also be seen in patients with congestive heart failure (CHF), toxic metabolic encephalopathy, or brain stem pathology. Actively dying patients have also been observed to demonstrate this breathing pattern.

Assuming that the opioids administered were not responsible for causing or exacerbating his Cheyne-Stokes breathing, the next question we should ask is as follows: Are opioids effective in reducing or abolishing this abnormal respiratory pattern? At least one report suggests that opioids may mitigate oscillatory breathing patterns in patients with CHF by decreasing peripheral chemosensitivity thought to be involved in the genesis of this breathing pattern.[8]

Regardless of whether the opioid exposure was the proximate cause for the patient's breathing pattern, he was, nonetheless, exposed to high doses of two strong opioids that were ineffective in abolishing the

observed breathing pattern for which they were intended. Moreover, the patient's impaired mental status might be attributable to opioid-induced neurotoxicity.

There also is concern that further titration or even continuation of this treatment plan may hasten the patient's death. The principle of double effect would allow for such foreseeable but unintended consequences of medications as long as the primary intention is to relieve the patient's suffering. Although some commentators believe that the emphasis on intentionality is problematic,[9,10] the principle of double effect has provided moral justification for using high-dose opioids for refractory symptoms at the end of life.[11–13] Perhaps, more importantly, the clinician should determine if the patient's suffering is indeed refractory to standard approaches (proportionality) and make sure that the decision to use sedating doses of medications is consistent with the patient's wishes (autonomy).[10,14]

In this case, it is not obvious that the patient's dyspnea—a subjective feeling of "air hunger" or "shortness of breath"—was truly refractory to low-dose morphine, requiring rapid escalation of two opioids to sedating doses. Indeed, the primary "symptom" the team attempted to alleviate was actually an aberrant breathing pattern interpreted as respiratory distress. Given the patient's level of consciousness, it is unlikely that the observed Cheyne-Stokes breathing pattern was causing any distress. Additionally, although the medical team and ethics consultant had a meeting with the family in which they agreed to focus on the patient's comfort, it is not clear to what extent the family gave consent to use sedating doses of pain medications.

Should the patient's sedation be considered an example of iatrogenic harm? Was it a result of medical error? If so, should this be disclosed to the patient's family?

An adverse event, or iatrogenic harm, is defined as "an injury that was caused by medical management rather than the patient's underlying disease."[15] A medical error is "the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim."[15] When a medical error is identified, the attending physician responsible for the care of the patient should disclose the error to the patient and/or family, apologize, and take steps to prevent its occurrence in the future.[15] Adverse events are not always the result of an error or a system failure. Examples of so-called "nonpreventable harms" are the side effects of common treatments or hazards of high-risk therapy, for example, chemotherapy.[15]

In this case, the patient likely experienced an adverse event from the high-dose opioid infusions, namely, deep sedation, and was at high risk of developing worsening neurotoxic side effects. It is not certain that the Cheyne-Stokes breathing was an adverse event of opioid exposure, but it was a *possible* iatrogenic harm. However, the adverse event in this case does not appear to be the result of a medical error and, thus, should not be disclosed as such. The planned action of the team was to use opioids to alleviate respiratory distress and provide a comfortable death. Unfortunately, the orders were vague: "titrate to comfort" with a wide range of drip rates possible, allowing caregivers to rapidly increase the dose infused per hour. In addition, the patient's abnormal breathing pattern was perceived as distressful to family and staff; hence, opioids were used liberally and titrated rapidly.

Unlike many medical treatments, for example, antibiotics for community-acquired pneumonia, where the correct choice of drug and the appropriate dose are easily discerned, pharmacological treatments for pain and other distressing symptoms at the end of life are not clearly defined, but rather depend on the nature of the symptom, the responsiveness of the patient, and the clinician's judgment regarding optimizing therapy. When patients are unable to communicate and the goal is to focus on comfort, clinicians tend to err on the side of providing more, rather than less, pain medication to insure that patients do not suffer unnecessarily. Currently, specialists in palliative medicine define the standard of care for pain and symptom management at the end of life. Once the standard of practice ("plan") is defined in hospitals through policies or specific guidelines, then medical error can be determined as nonadherence or unjustified deviation from such policies and practice guidelines (i.e., using "the wrong plan to achieve an aim"). When such errors occur at the end of life, they require timely and compassionate disclosure to families. The dying patient's safety should be no different from any other patient in the hospital.

Organizational Ethics Perspective

Without clear guidance for how and when to write opioid infusion orders, hospital staff may feel overwhelmed when faced with a dying patient whose exclusive goal is comfort. Palliative care specialists should educate clinicians and nurses in the proper use of opioid infusions at the end of life. It may be necessary to establish hospital policies and nursing guidelines to ensure that such practices are adhered to and become entrenched in the hospital culture. Guidelines should include the rationale for using opioids in patients at the end of life. Specifically, there should be guidance regarding how and when to initiate and titrate an opioid infusion. Orders for opioid infusions that state "titrate to pain relief" or "titrate to comfort" are clinically vague and place responsibility for dose titration exclusively on nurses. In addition, such orders do not give any guidance regarding how quickly to titrate or when to use bolus doses. Lastly, they expose the patient to potential toxic side effects when the dose is rapidly titrated.[16]

Case Resolution

The palliative care consultant suggested tapering the opioids and observing any changes in respiration pattern, level of sedation, and overall comfort. The patient was rotated to an equianalgesic dose of intravenous methadone, and the dose was reduced each day. No signs of pain or agitation were noted with tapering doses. The patient continued to remain deeply sedated, with apneic breathing episodes. He passed away three days later.

After this case, an ad hoc committee was formed to create a policy for the rational use of opioid infusions at the end of life. In addition, an education initiative has been launched throughout the hospital, targeting nurses and house staff on the proper use of opioid boluses and infusions for dying patients.

Conclusion

Careful weighing of the risks and benefits of opioid infusions need to be considered and routinely assessed in patients whose goal of care is no longer life prolongation but rather a focus on comfort. Palliative care specialists should work to provide guidance in their respective institutions by educating clinicians when and how to order and titrate opioid infusions for dying patients; the creation of policies and guidelines may be a necessary step to standardize the practice. Once established guidelines exist, nonadherence or unjustified deviation from them will be considered errors in patient care and should be disclosed. Patients at the end of life are particularly vulnerable and are at risk of adverse events. Every effort should be made to protect them from unnecessary harm.

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References

1. Leape L. Errors in medicine. Clin Chim Acta 2009;404(1):2–5.

2. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. J Clin Sleep Med 2007;3(5):455–461.

3. Farney RJ, Walker JM, Cloward TV, Rhondeau S. Sleep-disordered breathing associated with long–term opioid therapy. Chest 2003;123:632–639.

4. Teichtahl H, Prodromidis A, Miller B, Cherry G, Kronborg I. Sleep-disordered breathing in stable methadone programme patients: a pilot study. Addiction 2001;96(3):395–403.

5. Tarakanov IA, Tikhomirova LN, Safonov VA. Effect of opioids on mechanoreflexive respiration control. Bull Exp Biol Med 2005;139(4):388–390.

6. Farney RJ, Walker JM, Boyle KM, Cloward TV, Shilling KC. Adaptive servoventilation (ASV) in patients with sleep disordered breathing associated with chronic opioid medications for non-malignant pain. J Clin Sleep Med 2008;4:311–319.

7. Shook JE, Watkins WD, Camporesi EM. Differential roles of opioid receptors in respiration, respiratory disease, and opiate-induced respiratory depression. Am Rev Respir Dis 1990;142:895–909.

8. Ponikowski P, Anker SD, Chua TP, et al. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. Circulation 1999;100(24):2418–2424.

9. Brody H. Causing, intending, and assisting death. J Clin Ethics 1993;4:112–117.

10. Quill TE, Lo B, Brock DW. A comparison of voluntarily stopping eating and drinking, terminal sedation, physician-assisted suicide, and voluntary active euthanasia. JAMA 1997;278(23):2099–2104.

11. Foley KM. Pain, physician-assisted suicide, and euthanasia. Pain Forum 1995;4:163–178.

12. American Board of Internal Medicine End of Life Patient Care Project Committee. Caring for the dying: Identification and promotion of physician competency. Philadelphia, PA: American Board of Internal Medicine, 1996.

13. Council of Scientific Affairs, American Medical Association. Good care of the dying patient. JAMA 1996;275:474–478.

14. Morita T, Chinone Y, Ikenaga M, et al. Ethical validity of palliative sedation therapy: a multicenter, prospective, observational study conducted on specialized palliative care units in Japan. J Pain Symptom Manage 2006;25:103–105.

15. When things go wrong: Responding to adverse events. Boston, MA: Massachusetts Coalition for Prevention of Medical Errors, 2006.

16. Weissman DE. Fast facts and concepts #72: Opioid infusion titration orders, 2nd ed. End-of-Life/Palliative Education Resource Center, Medical College of Wisconsin, 2006. Available from http://www.eperc.mcw.edu.