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Fatal Patient-Controlled Analgesia (PCA) Opioid-Induced Respiratory Depression

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Case Objectives

- Describe risks associated with intravenous opioid administration through patient-controlled analgesia (PCA)
- Identify patient populations at high risk for postoperative opioid-induced respiratory depression
- Discuss best practices for PCA prescribing and administration
- Discuss best practices for monitoring sedation and respiratory status in postoperative patients receiving opioid PCA

The Case

A 69-year-old man with a history of cervical stenosis, coronary artery disease, chronic kidney disease, and hypertension developed worsening neck pain in the previous year, which prevented him from working, performing household tasks, and socializing with friends. Due to severe osteoarthritis and pain in his knees, he used a motorized scooter. The patient was admitted for elective surgery for decompression and to extend a prior C3-C6 fusion down to T3. Surgery was performed which concluded at approximately 13:00. The patient recovered in the post-anesthesia care unit (PACU), where he was placed on hydromorphone patient-controlled analgesia (PCA) for pain control and also received his usual home doses of gabapentin and acetaminophen. The patient was transferred from the PACU to the surgical floor at 20:00 where supplemental oxygen was placed for a peripheral oxygen saturation measurement (SpO_2) of 88%. The patient was awake and participating in care until 02:45. At 04:05, the patient was found unresponsive and a Code Blue was called. He was initially responsive to resuscitation efforts, and was transferred to the intensive care unit, where he arrested twice more. Tests the next day confirmed brain death and ventilatory support was withdrawn.

The Commentary

By Sarina Fazio, PhD, RN and Rachelle Firestone, PharmD, BCCCP

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) is widely used for postoperative intravenous opioid administration to promote pain management by enabling patient control of medication administration frequency. PCA involves opioid administration via an infusion pump that delivers a preprogrammed dose of opioid when the patient pushes a demand button with or without a constant-rate background infusion.[1] A lockout interval on the demand dose, usually 6-15 minutes, helps prevent overdose, as well as “dose stacking”, and can be adjusted depending on the opioid chosen and patient-specific factors such as opioid tolerance and risk for respiratory depression.[2] The PCA method avoids the peaks and troughs of analgesia typically seen with as needed (PRN) opioid administration and allows for more individualized dosing to achieve a predictable pain relief response.[3] Common side effects of opioid administration delivered through PCA include nausea and vomiting, pruritis, sedation, confusion, and respiratory depression.[2,4]

Opioid-Induced Respiratory Depression

Opioid-induced respiratory depression involves a combination of decreased respiratory drive, decreased level of consciousness, and upper airway obstruction due to a decrease in supraglottic airway tone.[5] In a 2018 review, the cumulative incidence of opioid-induced respiratory depression in postoperative patients was reported to be between 0.1% and 23.7%, due to variations in respiratory depression definitions.[6] The criteria for defining opioid-induced respiratory depression can include respiratory rate less than 8–10 bpm, SpO_2 less than 90%, airway obstruction, over-sedation, naloxone administration, respiratory arrest and/or cardiopulmonary resuscitation.[6] Additionally, the true incidence of opioid-inducted respiratory depression

may be challenging to determine because respiratory depression can resolve without leading to a sentinel event.

For many patients, while PCA is considered safer than continuous intravenous opioid administration, and has fewer logistical considerations than epidural analgesia, it can result in critical respiratory depression events with significant consequences.[7] PCA is associated with some risk of opioid-induced respiratory depression leading to significant morbidity and mortality.[8-11] From 2002 to 2011, the incidence of postoperative opioid overdose doubled from 0.6 to 1.1 per 1000 operative cases.[12] In a review of claims made between 1990 and 2009 from the Anesthesia Closed Claims Project Database, 26% involved likely opioid-induced respiratory depression, of which 77% resulted in severe brain damage or death.[13] Most of these opioid-related injuries occurred within 24 hours of surgery and were deemed to have been preventable with better monitoring and clinician response. Another review of nationally reported opioid-related sentinel events concluded that over 75% of all events were attributed to either medication errors involving wrong dose or improper monitoring.[14]

The overwhelming majority of PCA errors, which can occur at any phase of the medication-use process, are associated with human factors.[15,16] These errors are associated with prescribing (incomplete or contradictory orders, failure to adjust for organ dysfunction or comorbid conditions), dispensing (compounding errors, look alike/sound alike errors), and administration (pump mis-programming for drug, dose, or concentration; lack of continuous monitoring).[15] As a result of the preventable morbidity and mortality associated with opioid-induced respiratory depression in acute care hospitals, The Joint Commission released an alert in 2012[14] recommending that institutions implement policies and procedures to minimize the risk of respiratory depression associated with opioid administration.

Best Practices in Opioid PCA Use

Due to the significant risks of mortality and morbidity associated with opioid PCA administration, many best practices have been recommended. These best practices include, but are not limited to, comprehensive identification and assessment of high-risk patients, standardized guidelines for PCA prescribing and administration, and ongoing patient monitoring of oxygenation and ventilation, as summarized below.

Identification and Assessment of High-Risk Patients

Risk factors for opioid-induced respiratory depression associated with PCA among postoperative patients include patient-, comorbidity-, and surgical-related risk factors.[7,17,18] Table 1 summarizes the risk factors identified in each category. Patient-related factors include advanced age, female sex, and opioid dependence.[6,19] Specifically, preoperative use of gabapentin (greater than 300 mg) and sustained released oxycodone (greater than 10 mg) were associated with opioid-induced respiratory depression among patients undergoing orthopedic surgery.[20] Comorbidities such as obstructive sleep apnea (OSA), renal disease, pulmonary disease, cardiac disease, neurological disease, and obesity also are associated with increased risk of opioid-induced respiratory depression.[6,19,21] Analysis of the Anesthesia Closed Claims Project revealed that 45% of patients with respiratory depression had confirmed or suspected OSA

and 66% were morbidly obese.[13] OSA is also common among patients with fatal respiratory depression. A retrospective study of general surgery patients who died as a result of opioid-induced respiratory depression found that 50% had OSA.[22]

Table 1. Risk Factors for Opioid-Induced Respiratory Depression

Patient Characteristics	Comorbidities	Surgical & Perioperative
• Age > 55 years • Female gender • American Society of Anesthesiologists (ASA) physical status classification III-V • Opioid-dependent • Carrier of a risk-related genetic polymorphism • Smoker	• Confirmed or suspected obstructive sleep apnea (OSA) • Renal disease • Pulmonary disease (including COPD) • Cardiac disease (including CAD, CHF, arrhythmias) • Diabetes mellitus • Obesity (BMI > 30 kg/m^2) • Hypertension • Neurologic disease (including stroke, dementia) • Liver disease	• First 24 hours after surgery • Orthopedic, general, and transplant surgery • Prolonged surgery (> 2 hours) • Patient-controlled analgesia (with basal rate) • Inadequate monitoring and handoff communication • PACU respiratory events (including desaturation, apnea, hypoventilation) • Hours between 12 am – 6 am

Table adapted from Gupta 2018[6] and modified with risk factors presented in the following references: Jazyrna 2011[18], Arozullah 2003.[21]

Identification of patients at higher risk for opioid-induced respiratory depression prior to surgery has been recommended, especially to assess for OSA. The STOP-BANG questionnaire is an 8-item tool to screen for OSA (www.stopbang.ca/osa/screening.php).[23] The tool assesses a patient's risk for OSA based on a score calculated from questions related to snoring, daytime fatigue, waking up at night, hypertension, body mass index (BMI), age, neck circumference, and gender. Calculation of BMI and serum bicarbonate level is also recommended to screen for obesity hypoventilation syndrome, which additionally puts patients at risk for opioid-induced respiratory depression.[24]

In the case described, the patient had multiple risk factors for an opioid-induced respiratory event: age > 55, elevated serum creatinine level, and home use of gabapentin. The risk of a postoperative respiratory event might have been reduced by preoperative evaluation for OSA using the STOP-BANG questionnaire and development of a risk-based postoperative pain management plan before surgery.

PCA Prescribing and Administration

The safety of opioid use in high-risk patients can be improved through development of standardized pain order sets that highlight proper patient selection (opioid-naïve versus opioid-tolerant), emphasize oral opioids, and utilize multi-modal pain management strategies.[16] When PCA is used as the modality of choice, additional safeguards are necessary to prevent patient harm due to the complexity of the process (Table 2). For all types of PCA, the following variables must be prescribed by a provider and programmed by staff: drug concentration, initial loading dose, demand dose, lockout interval, and background infusion rate.[2] Each of these steps contributes opportunities for error. Additional risks include activation of PCA by others (usually well-meaning family, or "PCA by proxy") and equipment failure.[25,26]

Table 2. Best Practices for Opioid PCA Use

Prescribing	Dispensing	Administration
• Standardized PCA order sets • Dose in mg or mcg (not mL) • Reserve hydromorphone for opioid-tolerant patients • When choosing demand dose and lockout interval, consider concomitant sedating medications on profile • Set maximum dose limits with alerts	• Have a single concentration option for each opioid • Assess pump guardrails for hard and soft limits • Use pre-made or commercially available products when possible • "Tall man" lettering on pharmacy-applied labels	• Dual signature verification with double-check by 2 RNs to verify proper PCA connection and settings for new administration, rate change, assumed care, or change of shift • Connection between IV and PCA should be as close to the patient's venous access site as possible • Avoid administering concomitant opioids • Ensure availability of oxygen and naloxone • ETCO2 use (capnography) • Teach patient and family about the proper use of PCA prior to initiation

Table adapted from ISMP 2003[8] and the San Diego Patient Safety Council Tool Kit 2009.[27]

Implementation of standardized PCA order sets has been shown to mitigate risks associated with PCA and decrease the incidence of respiratory depression events.[28,29] Order set standardization should leverage clinical decision support to guide opioid selection, doses, and lockout periods, and should include embedded rescue naloxone orders. Given its potency and availability in high concentration, hydromorphone is ideally suited for opioid-tolerant patients but should be avoided as a first-line opioid choice for opioid naïve patients.[2,8]

In the case described, the patient was prescribed hydromorphone PCA without a continuous basal rate. Several important policy changes were made at an institution level in response to this fatal event, including

development of standardized pain order sets and guidelines for inpatient opioid administration. An educational emphasis was also placed on opioid selection for high-risk patients, with prompts to guide the prescriber based on patient-specific factors such as organ dysfunction and comorbid conditions such as OSA and renal insufficiency.

Postoperative Monitoring of Patients Receiving PCA

Patient monitoring involves regular observation, assessment and documentation of patient responses to opioid administration.[30] In postoperative patients receiving intravenous opioid PCA, vital signs, pain level, sedation status, and respiratory status, including oxygenation and ventilation, should be monitored and assessed (Table 3). A growing body of evidence and expert consensus support the use of capnography ($ETCO_2$) as well as pulse oximetry (SpO_2) to monitor patient oxygenation and ventilation.[31] Capnography measures the partial pressure of carbon dioxide in exhaled gases and can detect ventilatory abnormalities such as respiratory depression[32,33] before oxygen desaturation occurs, especially when supplemental oxygen is administered.[32,34-36]

Table 3. Monitoring for Patients Receiving Opioid PCA

Monitoring Component	Assessment Types
Vital Signs	Heart Rate
	Blood Pressure
Pain	Numeric Rating Scale
	Faces Pain Scale
	Iowa Pain Thermometer
Oxygenation	Pulse Oximetry (SpO_2)
Ventilation	Respiratory Rate (RR)
	Capnography ($ETCO_2$)
Sedation and Consciousness	Pasero Opioid Scale (POSS)
	Aldrete Score
	Glasgow Coma Scale
	Richmond Agitation-Sedation Scale (RASS)

Table adapted from Jungquist 2017.[30]

While continuous monitoring of oxygen saturation and capnography can help identify respiratory depression, recommendations for the timing and duration of monitoring can differ among organizations.[30] Societies agree that the timing of assessments should coincide with peak drug effects and that monitoring should occur more frequently for high risk patients.[37]

- The Anesthesia Patient Safety Foundation (APSF) recommends continuous monitoring of SpO_2 for all hospitalized adult patients receiving intravenous opioids for postoperative pain. For patients also receiving supplemental oxygen, APSF recommends continuous SpO_2 and $ETCO_2$.[31]

- A 2012 CMS Panel for PCA suggested that respiratory rate, sedation level, and SpO_2 monitoring should be performed every 2 to 2.5 hours.[38]

Patient-specific monitoring plans should reflect the type and route of opioid administration, post-procedural level of care, patient response to treatment and risk of adverse events.[30] However, evidence increasingly supports continuous monitoring of patients receiving intravenous opioids through PCA. In a recent systematic review,[39] the authors found that continuous SpO_2 monitoring on the surgical ward is associated with significant improvement in the detection of oxygen desaturation compared with intermittent nursing spot-checks. While the first 24-hours after surgery have the highest risk of opioid-induced respiratory depression, deaths most frequently occur overnight between 00:00-06:00 am when nurse staffing and monitoring frequency may decrease in an effort to promote sleep.[22,40] In 42% of cases reviewed in the Anesthesia Claims database, the interval between the last nursing assessment and detection of respiratory depression was less than two hours, further supporting the value of continuous monitoring.[13]

While recommendations related to monitoring for patients receiving PCA may vary, increasing the type and frequency of patient monitoring should be considered and discussed among members of the interprofessional team (MD, RN, PharmD) under any of the following circumstances:

- Evidence of desaturation, bradypnea, or hypoventilation (SpO2 < 93% or RR < 12 bpm or ETCO2 > 45 mmHg)
- Use of supplemental O_2, especially in the first 24 hours after surgery or between midnight and 6 am
- Increased sedation or change in level of consciousness (RASS = -2 or POSS =3)
- Presence of risk factors for opioid-induced respiratory depression, as outlined above
- Unrelieved pain or repeated attempts/demands within the lockout period despite patient education

In the case described herein, the patient was monitored at the prescribed monitoring intervals. However, the need for supplemental O_2 was a potential indicator that continuous SpO_2 and end tidal CO_2 monitoring would have been prudent. In addition, a standardized PCA handoff tool from the PACU to the surgical unit might have alerted the nursing staff to the patient's risk factors for opioid-induced respiratory depression.

Take-Home Points

- Opioid administration through PCA can result in fatal respiratory depression.
- Patients with obstructive sleep apnea and other comorbidities are at increased risk for postoperative respiratory depression.
- The first 24 hours after surgery and the hours between 12am and 6am hold the highest risk for fatal respiratory depression events.
- Continuous capnography and/or pulse oximetry should be used in all patients receiving PCA opioids for early detection of opioid-induced respiratory depression.
- Continuous capnography should be used in all patients receiving supplemental O_2.
- Interdisciplinary collaboration and communication are necessary to develop, implement and evaluate policies and protocols to guide safe opioid prescribing, administration, and monitoring.

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