Opioid Safety: Is Your Patient at Risk for Respiratory Depression?

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Case Study: S.J. is a 42-year-old woman with stage III ovarian cancer who underwent a total abdominal hysterectomy and bilateral oophorectomy today. Other than ovarian cancer, she has no other significant medical history except sleep apnea. She is five feet, two inches tall and weighs 200 pounds. Her serum creatinine and liver function tests are within normal limits. She was taking no medication prior to admission. Her medications now include hydromorphone (1 mg IV push every three hours as needed for pain) and promethazine (25 mg IV push every four hours as needed for nausea). At 1 am, she puts on her call light. “I really have a lot of pain. It is a 9/10, and I feel sick to my stomach. Could you get me something?” she says. Her last hydromorphone was four hours earlier, and she is due for promethazine. She is alert, and her respirations are 12. The nurse gives her hydromorphone and promethazine. One hour later, the nurse returns to the room and finds S.J. difficult to arouse. S.J.’s pupils appear constricted, and her respirations are 7 and shallow. The nurse notifies the resident on call and obtains an order for naloxone. The nurse administers the naloxone and oxygen and monitors the patient’s vital signs. S.J.’s respirations quickly return to normal, and she is alert and oriented.

Fear of respiratory depression is one of the major barriers to the effective use of opioids to manage pain. According to the American Pain Society (1996), withholding appropriate opioids based on respiratory concerns is unwarranted and leads to unnecessary suffering. Although death or neurologic injury for patients with otherwise treatable illnesses is tragic, serious complications from respiratory depression are not common. In most instances, clinically significant respiratory depression can be prevented by identification of high-risk patients, individualization of analgesic regimens, and close monitoring of respiratory and sedation status (Institute of Safe Medication Practices, 2002).

Pathophysiology

Most opioids commonly used in the clinical setting work primarily by binding to Mu receptor sites to produce analgesia. Mu receptors are located throughout the body, including the cerebrum and medulla (parts of the brainstem), which play an important role in respiration. Chemoreceptors in the medulla and other parts of the body detect low levels of oxygen (hypoxia) and high levels of carbon dioxide (hypercapnea). The body responds by increasing the rate and depth of respiration. Opioids bind to Mu receptor sites in the medulla and can cause respiratory depression. Naloxone, an opioid antagonist, is believed to bind to Mu receptors and reverse analgesia and other side effects of opioids, including respiratory depression (Sargent, 2002).

Definition

Clinically significant respiratory depression has been defined differently in the literature. McCaffery and Pasero (1999) defined it as a decrease in the rate and depth of respirations from a patient’s baseline. A meta-analysis examining postoperative pain management found that 70 study groups defined respiratory depression as fewer than 10 respirations per minute and 24 study groups defined respiratory depression as less than 90% oxygen saturation (Cashman & Dolin, 2004). Others have defined respiratory depression as fewer than eight breaths per minute (Sidebotham, Dijkhuizen, & Schug, 1997). A lack of correlation between respiratory rate and oxygen saturation level also has been reported (Hauer, Cram, Titler, Alpen, & Harp, 1995; Overdyk, Carter, & Maddox, 2006; Sidebotham et al.; Tsui et al., 1997).

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Incidence

The actual incidence of respiratory depression from opioids is unknown. The American Pain Society (1996) stated that respiratory depression from opioids is rare, a short-lived phenomenon, and most common in opioid-naive patients. A meta-analysis of 116 studies found the incidence of respiratory depression in 29,607 postoperative patients to be 1.1% (Cashman & Dolin, 2004). Shapiro et al. (2005) reported respiratory depression in 1.2% of 1,524 patients who received IV or epidural morphine for postoperative pain. Whipple et al. (1994) analyzed 4,669 postoperative patients receiving IV patient-controlled analgesia (PCA). Eleven (0.002%) clinically significant cases of respiratory depression were identified. A retrospective study of a database of 1,600 patients receiving IV PCA found eight cases (0.0113%) of severe respiratory depression (Etches, 1994). Schug and Torrie (1993) reported on 3,106 consecutive patients managed by an acute pain service. Treatable respiratory episodes in 16 patients (0.005%) all were recognized and managed rapidly. In another group, respiratory depression requiring naloxone was noted in 45 (0.09%) of 49,183 patients who received epidural opioids (Rawal & Allvin, 1996). Walsh, Rivera, and Kaiko (2003) examined the respiratory function of 20 hospice patients receiving oral morphine doses of greater than 100 mg per 24 hours. Respiratory rates, arterial blood gases, and peak respiratory flow rates were assessed. One patient (0.05%) had symptoms of ventilation impairment. The investigators concluded that morphine did not commonly cause chronic ventilation impairment when given to this population, even in the presence of respiratory disease.

Risk Factors

Although the literature often cites risk factors for respiratory depression from opioids, few studies have investigated incidence, predictive risk for respiratory depression, or whether combinations of risk factors increase patients’ incidence of respiratory events.

No tool for determining overall risk for respiratory depression from opioids was found in computer databases. Risk factors can be divided into patient characteristics and treatment-specific risk factors.

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Patient-Related Risk Factors

Advanced age: The aging process can affect the metabolism and excretion of medications, including opioids. Decreased renal and hepatic function can lead to the accumulation of drugs and metabolites, thus increasing toxicity. Taylor, Kirton, Staff, and Kozol (2005) found that patients older than 65 years were at increased risk for respiratory depression. Cepeda et al. (2003) conducted a retrospective cohort study with 8,855 patients aged 16 years or older who received short-term opioids. Of those patients, 1.5% experienced respiratory depression. The investigators found that, compared to patients aged 16–45 years, those aged 46–60 years had a 0.9 times greater risk for developing respiratory depression, those aged 61–70 years had a 2.8 times greater risk, those aged 71–80 years had a 5.4 times greater risk, and those older than 80 years had a 8.7 times greater risk.

Obesity: Obesity can lead to hypoxemia because of increased work to breathe and decreased lung capacity. PCA use in obese postoperative patients showed as much as a 10-fold range in dose requirements for overweight patients in the same weight range, possibly indicating the variability of drug metabolism in obese patients (Bennett et al., 1982).

Sleep apnea: Patients with sleep apnea who received opioids during surgery or in the postoperative period have been cited to have an increased risk for respiratory events, including sudden respiratory arrest (Etches, 1994; Parikh, Stuchin, Maca, Fallar, & Steiger, 2002). Ostermeier, Roizen, Hautkappe, Klock, and Klafta (1997) reported an absence of normal warning signals prior to sudden respiratory events in patients with sleep apnea receiving epidural opioids. The authors suggested that absence of normal warning signals could represent a critical difference between obese patients with sleep apnea and other patients being treated with epidural opioids.

Impaired renal, pulmonary, hepatic, and cardiac functioning: Taylor et al. (2005) investigated 62 postoperative patients who experienced a respiratory event following the administration of opioids and found that patients who had one or more comorbidities were at increased risk. Renal disease, chronic obstructive pulmonary disease, hepatic disease, and congestive heart failure have been reported as risk factors for respiratory depression from opioids (Flisberg, Rudin, Linner, & Lundberg, 2003; Taylor et al.). Impaired renal and hepatic function can affect the metabolism and excretion of many opioids, leading to prolonged exposure and increased side effects (McCaffery & Pasero, 1999). For example, morphine is conjugated in the liver, leading to two metabolites. One of the metabolites, morphine-6-glucuronide, can lead to respiratory depression (McCaffery & Pasero). For patients with impaired renal function, morphine and morphine-6-glucuronide excretion are delayed, causing prolonged exposure and increased risk for respiratory depression.

Sedation level: Sedation is a sensitive indicator. If left untreated, increasing sedation can lead to respiratory depression (McCaffery & Pasero, 1999). According to the American Pain Society (1992), “No patient has ever succumbed to respiratory depression while awake” (p. 23).

Patients in whom pain is controlled after a period of poor control: Pain stimulates breathing (Borgbjerg, Nielsen, & Franks, 1996). For patients who experienced poor pain control but then have pain suddenly controlled, the risk for respiratory depression may be increased (Pasero & McCaffery, 2002).

Treatment-Related Risk Factors

Opioid tolerance: Tolerance to opioids develops after a patient receives opioids routinely for a week or more (McCaffery & Pasero, 1999). Patients who are not opioid tolerant but are opioid naive are more likely to experience respiratory depression following administration of opioids (American Pain Society, 1996).
**Concurrent use of central nervous system depressants:** Combining anxiolytics, antihistamines, antiemetics, or muscle relaxants with opioids can produce excessive sedation that can progress to respiratory depression (Etches, 1994; McCaffery & Pasero, 1999). Promethazine, diphenhydramine, and lorazepam are such agents commonly used in oncology and often prescribed along with opioids.

**Postoperative day 1:** Taylor et al. (2005) found that 77.4% of 62 postoperative patients who had respiratory events following opioids had the respiratory events in the first 24 hours after surgery. Causes may be attributed to the combination of anesthetic agents, muscle relaxants, opioids, and other sedating medications, such as antiemetics.

**Nursing Management**

The keys to preventing life-threatening respiratory events from opioids are identifying high-risk patients, working with physicians and pharmacists to develop individualized analgesic plans based on identified risk factors, and systematically monitoring sedation and respiratory status.

**Individualized Plans Based on Risk Factors**

All patients receiving opioids should be assessed for risk factors (see Figure 1). Based on risk assessment, nurses should work with physicians and pharmacists to determine safe and effective medication regimens. When possible, potentially sedating medications (e.g., antiemetics, antihistamines) should be reviewed and replaced with less sedating medications. Route, duration, and frequency of medications should be changed if necessary. For example, older adult patients have been reported to have difficulty with IV PCA that includes a basal infusion (Lavand’Homme & De Kock, 1998). Medications that are metabolized by the liver and excreted by the kidneys (e.g., morphine) should be used cautiously in patients with hepatic or renal failure.

**Monitoring**

The type and frequency of monitoring may need to be adjusted for patients with risk factors. Pasero and McCaffery (2002) recommended monitoring sedation and respiratory status every one to two hours during the first 24 hours in opioid-naive patients treated for moderate to severe pain. Pain ratings, sedation levels, and respiratory status should be assessed before and after opioid administration; frequency should depend on the medication and route.

**Sedation scales:** Standardized sedation scales, such as the one offered by McCaffery and Pasero (1999) (see Figure 2), assist nurses in consistently assessing and communicating sedation. Pasero and McCaffery (2002) recommended choosing a sedation scale that is easy to understand and apply. In addition, they suggested the use of a tool that measures only sedation, not agitation or anxiety. In a recent review article addressing sedation scales, Chulay (2004) found only three sedation scales that had been tested for reliability and validity, but all three included patient factors (e.g., anxiety) in addition to sedation.

**Respiratory assessment:** The most accurate method for assessing respiratory status is controversial. Pasero and McCaffery (2002) stated that the best method for monitoring respiratory status is nursing observation of respiratory rate and depth. Assessments should be compared to a patient’s baseline, rather than set numbers. Pasero and McCaffery concluded that mechanical monitoring is warranted if a patient has risk factors for respiratory depression. Pulse oximetry and, less frequently, capnography (which measures carbon dioxide levels) sometimes are recommended to monitor respiratory status in patients at high risk. A lack of correlation among respiratory rates, pulse oximetry readings, and capnography has been reported. In a study examining 92 postoperative patients receiving PCA, Overdyk, Maddox, and Carter (2006) found that a low oxygen saturation level rarely correlated with a low respiratory rate. The investigators concluded that bradypnea is a poor predictor of desaturation and may be a late or absent finding in respiratory depression. Pulse oximetry may not be an accurate monitoring tool for patients receiving supplemental oxygen. Supplemental oxygen may prevent an oximeter from detecting low levels of oxygen in a timely manner (Overdyk, Maddox, et al., 2006; Fu, Downs, Schweiger, Miguel, & Smith, 2004).

**Conclusion**

Respiratory depression, although rare, is a potentially life-threatening complication of opioid use. By assessing patients’ risk for respiratory depression, nurses can work with physicians and pharmacists to develop individualized pain management plans and implement stringent monitoring of sedation and respiratory status.

**Case Study Discussion**

S.J. had numerous risk factors for respiratory depression, including obesity, sleep apnea, opioid-naïve status, and concurrent administration of a sedating medication (promethazine), plus it was...
her first postoperative day. The nursing staff caring for the patient should have identified the risk factors. The RN could have called the physician to discuss changing the antiemetic from promethazine to a less sedating medication, such as ondansetron. Although the effectiveness of pulse oximetry in detecting respiratory depression from opioids is not established, continuous pulse oximetry and frequent assessment of respiratory rate, depth, and sedation status may have led to earlier detection. The peak effect of hydromorphone occurs earlier than one hour after parenteral administration; therefore, the nurse should have assessed the patient sooner.

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References