

Importance of the correct diagnosis of opioid-induced respiratory depression in adult cancer patients and titration of naloxone

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ABSTRACT – Opioids can induce respiratory depression by invoking a centrally mediated decrease in involuntary respiratory rate, which in severe cases can cause a decrease in oxygen saturation. If respiratory depression is opioid induced, both low respiratory rate and low oxygen saturation will be present. If this is the case, oxygenation, rousing by verbal and physical stimulation and decreasing the opioid dose should be tried first. Naloxone, an opioid antagonist, should be avoided if at all possible but, if essential, titrate slowly to respiratory function administering 20–100 µg intravenously every two minutes. If used as a bolus for a patient on long-term opioids for chronic cancer pain, then refractory pain and symptomatic opioid withdrawal can result.

KEY WORDS: opioid, cancer pain, respiratory depression, naloxone

Introduction

Opioids are widely used in the management of cancer pain. Although they have a range of toxicities (Table 1), respiratory depression is the effect that is most concerning to physicians. In patients on chronic opioids for cancer pain, there is a need to ensure adequate oxygenation while maintaining analgesia and avoiding opioid withdrawal. Opioid-induced respiratory depression is centrally mediated. Animal and human studies, including neuroimaging, have shown that the central drive to respiration is generated in the brainstem, with carotid and aortic chemoreceptors sensing changes in blood oxygenation.^{1,2} When opioids induce respiratory depression, the respiratory rate is decreased (to less than 8 breaths/min) which, in severe cases, can lead to low oxygen saturation (<85%), high arterial pCO₂ values, and decreased ventilatory response to hypoxia and hypercapnea.^{3,4} The opioid receptor antagonist naloxone is the definitive treatment for this potentially life-threatening complication. However, naloxone reverses not only the toxicity of opioids but also their analgesia and can cause opioid withdrawal (Table 2), making the management of naloxone treatment difficult in patients with cancer pain. An accurate diagnosis of opioid-induced respiratory depression and its correct management is critical to patient care.

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Volunteer studies have illustrated that oxygen saturation is often maintained despite an opioid-induced decrease in respiratory rate. Intravenous remifentanyl almost halved the respiratory rate, but decreased SpO₂ by less than 3%.⁵ Similarly, sublingual fentanyl reduced respiratory rate (to as low as 5 breaths/min in one volunteer) but oxygen saturations never fell below 91%, and this was always manageable with breathing prompts.⁶ In patients receiving opioids for the relief of dyspnoea, there was no decrease in the oxygen saturation or increase in the CO₂ levels.^{7,8} The preservation of oxygen saturations might be due to an increase in tidal volume and conservation of minute ventilation.^{9,10} Thus, although respiratory rate is decreased, the overall ventilation and gas exchange remains stable, as do the oxygen saturations. In severe cases of opioid-induced respiratory depression, however, this compensatory mechanism fails and the patient can develop respiratory failure with a decreased respiratory rate and a subsequent decrease in blood oxygenation.

We report two representative patients to illustrate the importance of making a correct diagnosis of opioid-induced respiratory

Table 1. Side effects of therapeutic opioids.

System	Effects
Gastrointestinal	Constipation, xerostomia, nausea and vomiting, gastro-oesophageal reflux
Neurological	Delirium, hallucinations, sedation, myoclonus, hyperalgesia, seizures, headaches
Cardiovascular	Bradycardia, hypotension
Pulmonary	Respiratory depression, non-cardiogenic pulmonary oedema
Urological	Urinary retention, altered renal function
Endocrinological	Hypogonadism, sexual dysfunction, osteoporosis
Immune	T cell, natural killer (NK) cell, neutrophil and monocyte dysfunction, cytokine dysregulation (clinical effect unknown)

Table 2. Effects of naloxone administration and opioid withdrawal symptoms.

Common (unpleasant, not life-threatening)	Opioid-refractory pain, sweats, chills, headaches, muscle aches, joint aches, abdominal cramps, nausea, vomiting, diarrhoea, anxiety, fatigue, malaise, 'goose flesh'; similar to a severe flu-like illness
Rare	Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest

Box 1. Administration of naloxone for use in opioid-induced respiratory depression.

A standard ampoule containing naloxone 400 µg should be diluted to 10 ml with saline for injection. Every two minutes, 0.5–2.5 ml (20–100 µg) should be administered intravenously until the patient's respiratory status is satisfactory. Do not titrate to pain or conscious level.

suppression and the potential problems of using naloxone to completely reverse all the effects of the opioid, rather than just the dangerous respiratory effects.

Patients

Patient 1

A man with prostatic cancer and bone metastasis was on a stable dose of 50 mg of slow-release morphine twice daily. Two weeks following radiotherapy for hip pain, he was admitted as an emergency with a one-day history of shortness of breath and drowsiness. His respiratory rate was 41 breaths/min and his oxygen saturation was 80% on room air, this increased to 98% with 10 l/min O₂. Blood gases showed a pH of 7.5, pO₂ of 7.7 kPa and pCO₂ of 3.7 kPa. In view of the radiotherapy, the hypoxia was thought to be caused by opioid toxicity and the patient was administered 400 µg of naloxone intravenously. This did not help his dyspnoea but increased his pain and caused opioid withdrawal symptoms. He was subsequently diagnosed with a pulmonary embolus and several days passed before pain control was regained.

Patient 2

A woman with metastatic lung cancer had been deteriorating, without a reversible cause, in hospital and was awaiting transfer to a hospice for end-of-life care. She had been on a stable dose of 15 mg/day diamorphine subcutaneously for five days. One morning, she became increasingly sleepy and her breathing became shallow with a normal respiratory rate (18 breaths/min) and oxygen saturations of 88% on 4 l/min O₂. She was administered 400 µg of naloxone intravenously, which did not change her breathing rate but increased her pain level and caused agitation. She died a few hours later in pain.

Outcomes

For both patients, naloxone was administered to people on opioid therapy for cancer pain without evidence of opioid-induced respiratory depression (respiratory rate was greater than 8 breaths/min). Furthermore, naloxone was given as a bolus rather than titrating to respiratory effort, resulting in refractory reversal of the patients' opioid analgesia and withdrawal symptoms. Although Patient 2's medical team had identified that she was approaching the end of her life and were planning for this, they still did not recognise the natural processes of dying and did not take a palliative approach.

Discussion

The only definitive indication for intravenous naloxone in patients on therapeutic opioids is respiratory depression, as evidenced by a decreased O₂ saturation and respiratory rate that does not respond to verbal or physical stimulation and oxygenation. Acute reversal of opioid analgesia can be detrimental to the patient.

Optimal management plan

Confirm diagnosis

It is essential that opioid-induced respiratory depression is confirmed by observation of both a decrease in respiratory rate and impaired gas transfer with low oxygen saturation on pulse oximetry (or a low pO₂ and increased pCO₂ from arterial blood gases). The importance of considering other differential diagnoses for respiratory dysfunction in these cancer patients is essential. These include pneumonia, pulmonary embolism and multi-organ failure, which might present with a decrease in oxygen saturation but not a reduction in the respiratory rate; in fact, these patients are often tachypnoeic.

Conversely, a decrease in respiratory rate might not be associated with a decrease in oxygenation; hence, both reduced respiratory rate and a decrease in oxygen saturation are necessary for the diagnosis of respiratory depression.

Conservative measures

Consideration should be given as to whether the patient can be managed by conservative measures, such as rousing by verbal or physical stimulation, oxygenation (which may include bag and masking to remove CO₂), and possibly decreasing the opioid dose with careful monitoring. These may improve cerebral oxygenation and the patient's level of consciousness, enabling them to breathe spontaneously more effectively and avoiding the need for naloxone. Precipitating factors such as recent opioid dose increases or renal failure need to be identified and treated and dose adjustment must be considered.

Titration of naloxone

If naloxone is needed despite conservative measures, it should be titrated on an individual basis to obtain an optimal respiratory response while maintaining adequate analgesia. As naloxone has an onset of less than two minutes after intravenous administration, it should be given at a rate of 20–100 µg iv every two minutes, titrated to respiratory function not to the pain or consciousness level (See Box 1).^{4,11–13} This is a very different treatment to that for opioid-induced respiratory depression in intravenous drug users, for whom the aim is to reverse all the actions of the opioids using a 400 µg bolus. The elimination half-life of naloxone is approximately 60 minutes after intravenous administration. Thus, it might need to be administered several times to patients on an opioid with a long half-life and an iv infusion of naloxone might be required. The opioid used and

its dose also needs to be reviewed. If naloxone is needed by patients who are on chronic opioids for cancer pain, specialist advice should be sought regarding dose reduction and changing the opioid as, for example, buprenorphine might cause less respiratory depression than some other opioids.^{14,15} It is also essential to optimise the use of non-opioid analgesics.

In conclusion, opioid-induced respiratory depression, with low respiratory rate and low blood oxygenation, is potentially life threatening and emergency management is essential. While preserving oxygenation, the initial step of management is correct diagnosis, followed by conservative management if appropriate. If the hypoxia does not respond to this, then intravenous naloxone, titrated to respiratory effort, might be needed. Naloxone is not, however, without risk for the patient taking long-term opioids for cancer pain as it has the potential to cause opioid withdrawal and opioid refractory pain. Thus, it is vital to ensure the correct diagnosis and to try more conservative management if appropriate before using naloxone.

Competing interests

All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work. There was no additional funding.

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