Killing the symptom without killing the patient

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Many clinicians want to treat pain and dyspnea adequately but are concerned about opioid safety. Two questions in particular are clinical stumbling blocks for the appropriate and effective use of opioids in serious illness:

- Do opioids cause respiratory depression, especially in patients with cardiopulmonary disease?
- Do opioids shorten life when required to treat severe symptoms? In other words, can you kill the symptom without killing the patient?

Respiratory depression and opioids

Mrs T. is a 78-year-old woman with a 60-pack-year smoking history. She has advanced chronic obstructive pulmonary disease (COPD), with a forced expiratory volume in 1 second of less than 30% of predicted and a forced expiratory volume in 1 second–forced vital capacity ratio of less than 0.7. She is dyspneic with minimal activity despite maximal inhaled bronchodilators, steroids, and continuous oxygen. She is confined to her house and needs assistance with activities of daily living. She also has moderate congestive heart failure and mild chronic renal failure. Mrs T. is cognitively intact.

Mrs T. continues to complain of shortness of breath. According to the Canadian COPD guideline,[1] opioids are indicated for the treatment of refractory dyspnea in advanced disease. She is prescribed 0.5 mg of hydromorphone every 4 hours, with a 1-mg dose at bedtime to avoid middle-of-the-night dosing. Her family keeps in touch with her and drops in frequently to see how she is doing.

What is the risk of respiratory depression in this woman with advanced cardiopulmonary disease? Is this safe?

There are many small studies showing the safety of opioids when used in appropriate doses for pain and dyspnea in those with advanced disease. Double doses of short-acting opioids at bedtime (to avoid waking up to take the middle-of-the-night dose) do not appear to increase overnight deaths.[2] A review article in 2002 looked at multiple studies and found opioids could be used safely in dyspnea even with patients who had cardiopulmonary disease.[3] A UK study showed that the respiratory rate was not changed by morphine given for breathlessness to patients with poor respiratory function.[4] Injections of morphine given subcutaneously to patients with restrictive respiratory failure did not change their respiratory rate, respiratory effort, arterial oxygen levels, or end-tidal carbon dioxide levels.[5] Even when appropriate doses of opioids are given intravenously, respiratory depression is not seen.[6]

Despite this evidence, respiratory depression with the use of opioids does occur, and we all know of cases in which their use in a medical setting has resulted in death. Opioids can impair central nervous system respiratory drive resulting in alveolar hypoventilation and inability to adequately eliminate carbon dioxide and eventually to adequately exchange oxygen. The persisting confusion is that respiratory depression is not precisely defined, and many clinicians are not clear on what it is.

Respiratory depression is defined as a rise in peripheral P_{CO_2} and a fall in peripheral oxygen, as well as a reduction in the rate of respiration.[7] It is always preceded by sedation, and the process of sedation through to reduction and cessation of breathing takes at least 5 to 15 minutes. In a literature review, the incidence of respiratory depression in the management of acute moderate to severe pain via intravenous, epidural, subcutaneous, and oral routes in more than 27 000 patients was 0.5% or less.[8] This study, as well as others, recognized that respiratory depression was often not defined in the studies reviewed, and the incidence of true respiratory depression was likely even lower.

A 2008 study on patients with dyspnea due to advanced cancer, COPD, and amyotrophic lateral sclerosis measured respiratory rate, P_{CO_2} and oxygen saturation, and subjective dyspnea.[9] Patients were divided into either an opioid-naïve group (ie, no regular opioid use) or a group consisting of those who were already using regularly administered strong opioids for pain or dyspnea. Patients were monitored at baseline, 15, 30, 60, and 90 minutes after being given a short-acting opioid to treat the dyspnea. There was a significant reduction in subjective dyspnea ($P<.001$), as well as a significant reduction in the respiratory rate ($P<.0001$); however, there was no significant change in the oxygen saturation or P_{CO_2} at any time. It is postulated that opioids reduce dyspnea by reducing the workload of breathing, and the application of appropriate doses of opioids does not cause respiratory depression. Similar small studies on opioids in dyspnea have found similar results.[10-12]

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Hastened death and opioids

Mr B. is an 83-year-old man who is admitted to acute care 10 days after developing a productive cough. He has moderate to severe COPD and pulmonary fibrosis, and he has had 4 episodes of pneumonia in the past year. He has a history of hypertension, mild congestive heart failure, vascular dementia, and depression.

His admitting diagnosis is left upper lobe pneumonia and congestive heart failure, and he is treated with antibiotics and diuresis. He becomes increasingly confused and agitated during his stay. On the 10th day he develops sudden increasingly severe dyspnea and decreasing oxygen saturation. Chest x-ray and computed tomographic scans reveal acute respiratory distress syndrome. He is given an immediate dose of intravenous prednisolone. Mr B. is not a candidate for ventilation in the intensive care unit, so a decision is made to treat him symptomatically in addition to the steroids.

On examination he is in a high Fowler position and tries to lift himself up even higher. "I can't breathe," he says, in an agitated and distressed tone. His wife and daughters are by his side, exhausted and distressed. He is on high-flow oxygen, but he keeps trying to remove it. Measurements of his vital signs reveal the following: respiratory rate of 32 breaths/min, blood pressure of 129/60 mm Hg, and oxygen saturation of 90% on high-flow oxygen. After a discussion with Mr B.'s family, a 10- g-per-hour fentanyl infusion is started at 6:00 PM, with breakthrough doses of 2 g given every 15 minutes.

The nurse reports that Mr B. has calmed down and that his dyspnea has improved. At 6:45 PM, measurements of his vital signs reveal the following: respiratory rate of 24 breaths/min, blood pressure of 120/54 mm Hg, and oxygen saturation of 89% on high-flow oxygen. After a brief nap, Mr B. wakes up and eats—the first time he has eaten all day. His family sees that he is calmer, and they are able to go home for a rest. At 7:00 PM a decision is made to transfuse 2 units of packed red cells, as his hemoglobin level has fallen from 91 g/L to 71 g/L over the past several days. At 7:30 PM, measurement of his vital signs reveals a respiratory rate of 28 breaths/min, blood pressure of 118/67 mm Hg, and oxygen saturation of 85%. The nurse notes that he is calm and not agitated. He has received 5 breakthrough doses of the fentanyl since the start of the infusion.

At 10:00 PM Mr B. sees the nurse in the room and asks her to call his daughters. He then becomes unresponsive—his eyes stare straight ahead and he breaths in agonal-type gasps. His blood pressure is 64/50 mm Hg, and his heart rate is irregular and thready. The resident is called and she gives Mr B. 3 doses of 0.4 mg of naloxone, with no effect. The patient dies at 10:25 PM. Both the nurse and the resident are concerned that the opioid has caused Mr B.'s death.

BOTTOM LINE

- Respiratory depression is often not precisely defined, and many clinicians are not clear on what it is. Respiratory depression is defined as a rise in peripheral PCO_2 and a fall in peripheral oxygen, as well as a reduction in the rate of respiration. It is always preceded by sedation, and the process of sedation through to reduction and cessation of breathing takes at least 5 to 15 minutes.
- Studies show that appropriate doses of opioids do not cause respiratory depression.
- Studies of the relationships between opioid dose, change of dose, and use of sedatives and time to death in patients with advanced illness have found no significant relationships.
- Giving naloxone to patients using opioids who are not experiencing respiratory depression can cause severe distress, as the symptom relief is suddenly reversed. If a patient is using opioids and respiratory depression is suspected, a 1 in 10 dilution of naloxone can be used to reverse respiratory depression without losing symptom relief.

POINTS SAILLANTS

- La dépression respiratoire n'est pas toujours définie avec précision et de nombreux cliniciens ne savent pas clairement ce qu'elle est. La dépression respiratoire désigne une élévation du pCO_2 périphérique et une chute de l'oxygène périphérique, ainsi qu'une réduction de la fréquence respiratoire. Elle est toujours précédée par la sédation et le processus de la sédation jusqu'à la réduction et la cessation de la respiration prend au moins de 5 à 15 minutes.
- Des études démontrent que des doses appropriées d'opioïdes ne causent pas la dépression respiratoire.
- Des études indiquent qu'il n'y a pas de relations significatives entre la dose d'opioïdes, le changement de dose, et l'utilisation de sédatifs et le moment du décès chez les patients à un stade avancé de la maladie.
- Administrer de la naloxone aux patients qui ne sont pas en état de dépression respiratoire peut causer une grave détresse, parce que le soulagement des symptômes est soudainement inversé. Si un patient utilise des opioïdes et qu'on soupçonne une dépression respiratoire, on peut diluer une partie de naloxone pour 10 afin de régler la dépression respiratoire sans compromettre le soulagement des symptômes.

The concern about opioids hastening death has been a long and persistent one. Studies of the relationships between opioid dose, change of dose, and use of sedatives and time to death in patients with advanced illness have found no significant relationships.[13-19] In a US study on withdrawal of patients from ventilators, opioids did not shorten the time to death and the use of sedatives seemed to prolong life.[20]

The largest study yet included 1306 patients with advanced disease who were admitted to 13 hospice programs across the United States.[21] The average length of stay and thus observation was 30 days. A total of 725 patients were using regular opioids and received at least one change in dose before death. The average time from final dose change to death was more than 12 days, which

rules out a direct effect from the opioids. There was a weak association between the final dose of opioid and time to death, but there was no relationship with the rate of change in dose. Multivariate analysis revealed that the total dose, disease severity, function, length of stay, and race were also associated with time to death. Opioid dose alone, and even in combination with the other factors, explained only a very small percentage of the variation seen in survival.

Giving naloxone to patients using opioids who are not experiencing respiratory depression can cause severe distress, as the symptom relief is suddenly reversed. If a patient is using opioids and respiratory depression is suspected, a 1 in 10 dilution of naloxone can be used to reverse respiratory depression without losing symptom relief.[22]

Mr B. likely died of a sudden cardiac arrhythmia or a pulmonary embolus—2 well-known complications of acute respiratory distress syndrome. He was alert, with normal vital sign measurements taken 30 minutes previously. His sudden deterioration with no preceding sedation did not match the clinical picture of respiratory depression. The ineffectiveness of 3 doses of naloxone confirms this.

Mr B.'s wife and daughters greatly appreciated seeing him calm and less short of breath when they last saw him alive. They understood how sick he was and that he was likely to die. He had been agitated, restless, and distressed for much of the past 10 days in hospital, and seeing him calm and less short of breath gave them comfort.

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Competing interests
None declared

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