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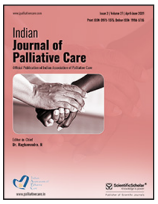

Case Report

Patient-Controlled Therapy with Intravenous Oxycodone in Breathlessness due to Advanced Cancer: A Case Report

Mahesh Radhakrishnan Menon[1], Shiv Pratap Singh Rana[1], Subashini Perumal[1], Khawla Fuad[1]

[1]Department of Palliative Care and Pain Management, Bahrain Oncology Centre, King Hamad University Hospital, Busaiteen, Bahrain.

ABSTRACT

Dyspnoea is a debilitating symptom in medicine, especially in palliative care. Opioids are the pharmacological agents of choice in the treatment of dyspnoea in palliative medicine. Morphine is the best-studied opioid, and recent literature on oxycodone is encouraging. In refractory cases, opioid infusion and palliative sedation may have to be used. We present a case that used oxycodone in a patient-controlled device specifically for dyspnoea and its effects in relieving dyspnoea in a fast and timely manner. This helped in meeting the demands of the patient and relieving suffering rapidly with less sedation. This case report is unique in the use of an oxycodone patient-controlled device specifically for dyspnoea.

Keywords: Intravenous patient-controlled therapy, Oxycodone, Dyspnoea, Breathlessness, Advanced cancer

INTRODUCTION

Dyspnoea is a powerful signal linked by years of evolution to the most primal neural circuits. Indeed, being aware of one's breathing and being distressed by this awareness can be a source of great suffering in patients with advanced disease. A prospective cross-sectional study of 500 outpatients at a palliative care clinic concluded the prevalence of dyspnoea to be as high as 44.37%, with a negative impact on quality of life.[1] Opioids have a vital role in the pharmacological measures used to reduce dyspnoea, possibly exerting their effect by various mechanisms as described in a recent Cochrane review:

1. Decrease in corollary discharge from the brainstem to sensory areas in the cerebral cortex
2. Blunting the perception of breathlessness, analogous to the action of opioids in pain relief
3. Peripheral actions on receptors in bronchioles and alveoli.[2]

Thus, palliative care teams may administer opioids by different routes to relieve breathlessness, and the present case report discusses the role of parenteral oxycodone, administered through a patient-controlled device.

CASE REPORT

A 17-year-old male with progressive metastatic osteosarcoma of the left lower limb, not responding to chemotherapy, was placed on best supportive care. He presented to the emergency department at 5 a.m. with acute worsening of breathlessness and constipation. He had lung metastases and was diagnosed with a pulmonary embolism recently, for which he was on anti-coagulation with enoxaparin 50 mg twice a day. He was being managed at home for breathlessness with oral morphine syrup 5 mg 12 hourly as needed pro re nata (PRN), and lorazepam 0.5 mg for insomnia and anxiety. He was on oxygen at home at 6 L/min and his symptoms were well controlled. He was bed bound, with a palliative performance scale version 2 (PPSV2) of 30%, with limited indoor mobility. He was spending time at home with family, and he loved to play video games.

He was in type 2 respiratory failure, with a respiratory rate of 42/min and an elevated partial pressure of carbon dioxide in blood gases, and his inflammatory markers were elevated. The emergency department and the respiratory medicine team ruled out other reversible causes of breathlessness after initial assessment and review. He was put on non-invasive ventilation and stabilised, and shifted to the ward. After admission, he was initially on a facemask with oxygen at a flow rate of 10 L/min, maintaining saturation at 95%. His breathlessness was reported as a 10 on a numeric rating scale (NRS). For this, we initially started him on oral morphine 10 mg 3 times a day, which did not help his symptoms; instead, it may have

***Corresponding author:** Mahesh Radhakrishnan Menon, Department of Palliative Care and Pain Management, Bahrain Oncology Centre, King Hamad University Hospital, Busaiteen, Bahrain. mahesh.rk@gmail.com

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caused him to experience dysphoria-like symptoms after the first dose itself. He mentioned that he did not 'like how he felt' with the drug. We had escalated the dose of morphine heuristically, keeping in mind the intensity of the patient's distressing breathlessness, apparent lack of response to lower doses, terminal nature of malignancy, and frequency of repeat hospitalisation. After this, he refused to take either injectable or oral morphine. We administered a 1 mg oxycodone bolus intravenously at 11:00 h and assessed his breathing difficulty in 15 min as per the policy for assessment of patients administered intravenous opioids. Mori *et al*., have discussed the use of parenteral oxycodone in breathlessness in their study.[3] In our practice, the guidelines by the British National Formulary and Palliative Care Formulary are followed in opioid dose conversions. Based on these, we converted the 5 mg oral dose of morphine to 2.5 mg oral oxycodone. We used the equianalgesic equivalence between subcutaneous: Oral oxycodone as 1.5:1, which yields us 1.7 mg subcutaneous for oxycodone. In our patient, we used a lower dose of 1 mg while starting the bolus doses on a conservative note. His dyspnoea improved significantly (NRS 3), and he was able to sleep better. He took another bolus dose later in the evening at 8:00 p.m. the same day. He relayed to us about his improvement in dyspnoea and better quality of night sleep during our morning rounds the next day. He was vitally stable, maintaining oxygen saturation above 94%, with continuous supplemental oxygen provided through nasal prongs or face masks with flow rates to target saturation of more than 94%. He preferred to use nasal prongs more than face masks. We observed that switching to the new opioid-oxycodone from morphine significantly relieved his dyspnoea and improved his quality of sleep with just two doses.

There was a striking clinical improvement in terms of his NRS and an improvement in the respiratory rate to 20/min from an initial rate of 42/min on admission. There was no further dependence on non-invasive ventilation. In the absence of clear criteria to guide opioid switching/drug delivery in dyspnoea, we relied on the work done by Schmitz *et al*.[4] This prompted us to start the patient-controlled device, with the intention of resolving his symptoms in a speedy manner and providing the patient with control and confidence in self-management of symptoms towards the end of life. The team programmed the oxycodone patient-controlled therapy (PCT) (Device: Rhythmic TM Evolution Blue) to administer an on-demand bolus dose of 0.5 mg intravenously and lockout for 5 min between doses, with no background continuous infusion. The 4-h limit for oxycodone usage was set at 30 mg. The assigned staff nurses routinely charted clinical parameters such as pulse, temperature, blood pressure, oxygen requirements, respiratory rate, pain scale, sedation scale, and amount of infused opioid medication from the patient-controlled pump in the electronic hospital patient-controlled analgesia observation chart every four hours. Patient monitoring frequency was based on early warning scores. With this device, his breathlessness remained controlled from 10 to 3 on a NRS. His sedation score was one on the Pasero opioid sedation scale.

During this hospitalisation, there was one occasion when there was an inadvertent delay in refilling the PCT device. When he was off the patient-controlled device, he experienced an episode of breakthrough dyspnoea, which resolved with a nurse-administered bolus of oxycodone 1 mg. This reinforced our decision to continue the patient-controlled device to maintain symptom control. His breathlessness remained controlled after restarting the device. His average daily oxycodone consumption remained around 19 mg (155 mg oxycodone consumed over eight days), and his breathlessness and distress remained under control throughout his hospitalisation till his death. Table 1 summarising the daily oxycodone consumption is provided below:

His distress and anxiety had significantly reduced during his admission. He tolerated oxycodone without major adverse events, and he developed confusion in the last few hours before his death as his respiratory failure worsened. His breathlessness used to be distressful for the parents, and controlling the patient's distress ensured that the family was able to spend quality time during admission.

At home and in the hospital, he would always monitor his oxygen saturation constantly with the pulse oximeter probe on his finger. He would become anxious if the probe was to be removed. During his stay, we were able to convince him to disconnect the pulse oximeter from his right index finger since he only needed intermittent monitoring when he was stable. On one of our morning rounds, we asked him to narrate how the patient-controlled device with oxycodone had helped him. He smiled after he removed the pulse oximeter probe from his finger, pointing to the iPad on his lap, and said, 'I can play video games better.'

DISCUSSION

The recent Cochrane review concluded that there was low-quality evidence for the use of opioids (oral and parenteral) in the palliation of dyspnoea.[2] Another meta-analysis concluded a low quality of evidence in favour of a small benefit of opioids.[5] A recent, more comprehensive narrative review of breathlessness and opioids in dyspnoea, done by Johnson and Currow, concludes that there is level 1a evidence to support the use of opioids.[6] Morphine remains the most studied opioid in the literature on breathlessness, and in the present case report, we titrated opioids from oral morphine to patient-controlled oxycodone administered intravenously.

Table 1: Total daily oxycodone consumption

Day	1	2	3	4	5	6	7	8
Drug utilised: Oxycodone (milligrams)	17	24	23	19	25	20	17	10

There are two placebo-controlled trials for oxycodone, which remain inconclusive. The first one used controlled-release oxycodone.[7] The second trial was of immediate-acting oral opioids in patients with heart failure who experience breathlessness.[8] We have observed that for patients who experience 'attacks' of breathlessness, in an analogous manner to 'breakthrough pain,' a controlled dose preparation that begins its action in 1 hour or oral preparations that may act after 10–15 min may not suffice. In contrast, the analgesic onset time of oxycodone is 2–3 min, which is as fast as that of intravenous fentanyl.[9] Studies in acute post-operative pain have also demonstrated a faster onset of action for injectable oxycodone compared with morphine.[10]

In the pilot study of 18 patients with refractory breathlessness and advanced disease by Schmitz *et al*., the use of patient-controlled treatment with opioids was deemed to be an acceptable therapeutic method.[4] The opioid used in this study was morphine. This study defined PCT as follows: 'Patient-controlled therapy is an interactive method of symptom management that permits patients to manage their symptoms by self-administering doses of drugs, usually opioids.' The authors mention the relevance of this treatment strategy in the context of the speed of amelioration of symptoms. In hospital settings, multiple factors may induce a time lag from when the patient experiences the symptoms to when the nursing team provides the medication or intervention. We agree with the authors and feel that these could be due to infrastructure, resource availability, and availability of trained personnel.

A multicentre prospective observational study by Mori *et al*., of terminal dyspnoea in cancer patients compared 26 patients who received parenteral oxycodone and 138 patients who received parenteral morphine.[3] It concluded that parenteral oxycodone may be equal to morphine in terms of effectiveness and safety as morphine.

Our case report highlights the role of patient-controlled oxycodone in patients who may not tolerate morphine or even use PCT with oxycodone as a first-line medication for use in refractory breathlessness. Indeed, a study on genetic factors found that people with rs7103572 single nucleotide polymorphism (SNP) (HTR3B gene; present in 8.4% of the population) were three times more likely to have more intense breathlessness (odds ratio: 2.86; 95% confidence interval: 1.46–5.62; $P = 0.002$).[11] However, there were no associations of SNPs with dyspnoea in patients treated with oxycodone or fentanyl.

Our study has limitations

1. It is observational
2. It is subjective, with the only measure of distress being the patient's self-reported scale
3. We cannot generalise this to the palliative care population with non-cancer conditions.

To the best of our knowledge, this is the first case report on PCT oxycodone for relieving dyspnoea in a cancer patient. We believe that this report highlights the need for more research on oxycodone in background, episodic, and refractory breathlessness in patients and encourages the use of PCT with oxycodone where possible.

CONCLUSION

We have highlighted the importance of patient-controlled devices in palliative care settings in the management of difficult symptoms like dyspnoea in terminal cancer patients. Patient control intravenous treatment offers rapid, effective, and personalised symptom control and the ability to titrate opioid doses to symptoms. We believe that this might provide valuable help to patients before escalation to continuous background doses of opioids.

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Ethical approval

The research/study is approved by Education and Proficiency Center Research and Ethics Committee King Hamad University Hospital, Application number KHUH-EPC-RE-RPAPPFORM Vl.0 /20.09.2017 Dated 3rd April 2023.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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