Case report

Nebulized fentanyl for refractory dyspnea secondary to chronic obstructive pulmonary disease (COPD): A case report

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ABSTRACT

We present a case where we evaluated the effectiveness of nebulized fentanyl in the treatment of refractive dyspnea in a patient with chronic obstructive pulmonary disease (COPD) with major complications and comorbidities. Nebulized fentanyl was used to successfully decrease the subjective symptoms of refractory dyspnea in this given patient. Nebulized fentanyl appears to be a cost-effective treatment option in patients that experience episodes of severe shortness of breath (SOB).

1. Introduction

Dyspnea is a common and debilitating symptom of cardiopulmonary and neuromuscular diseases [1]. Appropriate diagnosis and treatment of the underlying cause of dyspnea would be ideal but is not always a possibility [1]. Some patients experience idiopathic dyspnea, in which the etiology is unclear. Other patients continue to experience dyspnea even with appropriate treatment regimens; this is deemed “refractory dyspnea” [2]. Dyspnea is a common and debilitating effect of severe COPD, and a significant number of patients eventually fall into the “refractory dyspnea” category [2]. In advanced COPD, up to 94% of patients report that dyspnea significantly impacts their quality of life [3]. While some individuals with COPD may stabilize over time without significant symptoms, COPD is still the 4th leading cause of death worldwide and is often manifested as a progressive pulmonary disease that inevitably leads to palliation. Therefore it is important to be able to provide these patients with alternative treatment options in order to manage their symptoms [4]. In palliative care, innovative methods are often implemented to assist patients living with chronic diseases in reducing or relieving symptoms and ultimately improving quality of life.

In the terminally ill, systemic opioids are often administered as a treatment modality for dyspnea. Their mechanism of action works by decreasing spontaneous respiratory drive, modulating cortical activity, and diminishing the brainstem chemoreceptors response to hypoxia and hypercapnia [5]. Systemic opioids are associated with a plethora of adverse effects including: sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance and respiratory depression [6]. With the pathophysiologic knowledge that the lung contains active peptides (enzymes necessary for activation of opioids) and opioid receptors (μ, κ, and δ), it was presumed that nebulization of opioids would be effective by acting on those local peripheral neural receptors in the small airways of the lungs [2,5,7]. This local activity could reduce the incidence of adverse effects associated with systemic administration [5, 7].

For well over 20 years, morphine has been noted as the main stay of opioid therapy for refractory dyspnea [8]. However, few studies have evaluated other opioid agents for this indication. As of yet, there are no systematic reviews or randomized controlled trials showing a clear benefit of one inhaled opioid compared to another. Although there is limited data in the literature, nebulized fentanyl has been noted to have a positive impact on resolving dyspnea [9]. This case report explores the use of nebulized fentanyl in order to broaden therapy options for those experiencing refractory dyspnea.

2. Materials and methods

A retrospective electronic medical record chart review was performed in order to assess the symptom improvement after nebulized fentanyl administration in this patient case.

3. Results

RS is an 86-year-old male with a history of chronic obstructive pulmonary disease (COPD) (FEV1 32%) with major complications and comorbidities of: tracheobronchiomalacia, bronchiectasis, paroxysmal atrial fibrillation, hyperlipidemia, prostate cancer s/p prostatectomy,

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mild dementia, and gastroesophageal reflux disease who presented with acute on chronic respiratory failure. He was admitted 4 times over the course of a month and 8 times within the past calendar year, all with similar presentations. His typical presentation was tachypneic with a respiration rate in the upper 30’s, decreased bilateral breath sounds, accessory muscle usage, and wheezing. His respiratory failure was accompanied by a productive cough with green sputum that was chronic and present for months. Arterial blood gas results (ABG) had shown respiratory alkalosis on multiple previous admissions. On this admission, the ABG was as follows: pH 7.56, partial pressure of carbon dioxide 22 mmHg, partial pressure of oxygen 189 mmHg, bicarbonate 20 mEq/L. Electrolytes tested on admission were as follows: sodium 139 mEq/L, chloride 111 mEq/L, bicarbonate 21 mEq/L, and potassium 4.5 mEq/L. RS had been intubated 3 times in the past for reported COPD exacerbations. On this admission, he was at 100% oxygen saturation on 40% FiO2. There was no evidence of bacterial infection and all respiratory virus panels were negative to date. RS had an extensive workup to assess metabolic, endocrine, infectious, and central causes of hyperventilation but no source of tachypnea was discovered.

At home, RS was initially managed on home nebulizers of sodium chloride, albuterol, and budesonide/formoterol. However, he continued to present to the ED when the nebulizers failed to relieve SOB symptoms. Between discharges, his therapy began to intensify with the addition of supportive home O2 as needed (PRN) and PO morphine 5 mg q6hrs PRN air hunger. At the most recent discharge, RS was managed on sodium chloride nebulizer solution, morphine 100mg/5 mL concentrated solution (0.3 mL PO Q6HRS PRN), levobuterol nebulizer solution, and Symbicort. The patient’s home tested negative for mold and harmful air quality, and plans to remove carpeting to reduce irritant exposure were in place.

In order to manage RS’s symptoms inpatient, he often required bilevel positive airway pressure (BiPAP), that was weaned down to continuous positive airway pressure (CPAP) (used nocturnally), high flow nasal canula (HFNC), and then to room air. He completed various rounds of chest physiotherapy supplemented with humidified and heated air, fan-to-face, and breathing exercises. RS failed various therapies of bronchodilator treatments, mucolytic treatments, hypertonic saline, and corticosteroid inhalation treatments. Precedex was trialed with no improvement in symptoms; Precedex was then discontinued due to the anticholinergic risk associated with the medication. PRN 5mg IV morphine Q6hrs was used on admission to decrease agitation and assist in decreasing air hunger; however, it showed inconsistent benefit in relieving his SOB. This dose of morphine is within the normal range of morphine used for dyspnea as it may alleviate symptoms while potentially avoiding respiratory depression [10]. A psychiatry consult was conducted due to suspicions for anxiety as a cause of SOB, but it was concluded that RS did not suffer from depression or anxiety. However, there were still suspicions that situational anxiety caused the patient to further decompensate during his tachypnic episodes. Therefore, RS was trialed on a single dose of 0.1 mg oral lorazepam during an episode of dyspnea with improvement in symptoms. He was later started on a daily dose of 0.25 mg of oral clonazepam that was titrated up to the patient’s most recent dose of 0.5 mg daily.

PRN intravenous (IV) fentanyl was attempted with a reported adverse event of hallucinations. However, the patient noted that fentanyl provided the biggest improvement in subjective symptoms when compared to albuterol and morphine. A trial of nebulized fentanyl (25 mcg/mL of fentanyl citrate) was administered at home and the need to manage the acute and sudden onset of symptoms that arose without noted trigger. The nebulizer used was the Aerolact® II Breath Actuated Nebulizer. This nebulizer is reported to deliver medication with a mass median aerodynamic diameter of 2.8 μm (μm) [11]. Prior to nebulized fentanyl administration, RS scored a 10/10 on the Edmonton Assessment Scale; this assessment was either not repeated or not charted after medication administration. RS experienced significant subjective improvement in symptoms when nebulized fentanyl was administered.

After several instances of beneficial nebulized fentanyl administration, the patient requested to be sent home with a prescription for nebulized fentanyl in order to manage his symptoms in the outpatient setting and prevent further hospital admissions. RS and his caregiver noted on multiple instances that nebulized fentanyl had the biggest improvement on his symptoms. The caregiver was given education on the preparation and administration of nebulized fentanyl solution for home use. However, the patient presented to the Emergency Department with similar symptoms after his discharge; additional education was given at that time, as there was concern that the concentration administered at home was not accurate. The dose of his outpatient nebulized fentanyl was increased to 50 mcg every 4 hours. After the most recent education, the patient had not re-presented to the ED within 6 months.

4. Discussion

This case used a novel therapeutic approach of using nebulized fentanyl for refractory dyspnea in a patient with COPD with multiple comorbidities and complications. This patient continued to have dyspnea despite treatment with levalbuterol, concentrated morphine, and supplemental oxygen. Administration of nebulized fentanyl, an opioid agonist, could possibly decrease the incidence of potential adverse effects such as nausea, vomiting, and constipation associated with systemic opioid administration. As with this patient, and many others with debilitating chronic diseases, medication regimens are often extensive with the risk of each drug exhibiting side effects that further complicate patient care. Avoidance of adverse effects, which are often additive in nature, can be crucial in these patient populations.

Even with the positive effects reported by the patient and his caregiver (wife), it is important to take note of the limitations seen in this case report. By nature, a retrospective chart review is limited to what may be found in a patient’s chart. A significant limitation in this chart review is the inability to quantify how RS’ dyspnea changed after medication administration as the Edmonton score was not reported after medication administration. Another limitation in this report is the patient’s diagnosis of mild dementia. With this diagnosis, it is unclear how able RS was to accurately compare the perceived benefit from nebulized fentanyl compared to his other treatment modalities. However, the nurses and caregiver noted benefit in his SOB and he did not re-appear to the hospital after being discharged with nebulized fentanyl. These factors increase the reliability of the findings that this patient benefitted from nebulized fentanyl.

Medication cost can play a vital role in selecting drug therapies. The price for the vials of fentanyl is fairly cost effective. The wholesale acquisition price (WAC) for our given institution’s outpatient departments is $1.14 for fentanyl citrate 50mcg/mL in 2 mL single use vials. In the case that insurance does not cover the cost of fentanyl vials, a pack of 25 vials would be sold for $44.00. The inpatient WAC price is $0.55 per vial. Nebulized fentanyl is similarly priced to oral morphine, which has been used for air hunger over the past few decades. Concentrated morphine sulfate oral solution 100 mg/5mL costs an average of $0.84 per mL at our given institution. Utilizing this patient’s previously failed outpatient regimen of morphine sulfate 100mg/5mL taking 0.3 mL every 6 hours as needed, an estimated monthly cost would be approximately $30.24. Avoiding the astronomical prices that are often associated with novel drug therapies is an added benefit for utilizing nebulized fentanyl. Nebulized fentanyl could be beneficial in a palliative care setting, where patients have refractory dyspnea.
from COPD. The patient and his caretaker (wife) in this case reported improvement in his SOB, and therefore increased quality of life. Administration by the nebulized route avoided the systemic adverse effects that are often associated with opioids. The cost effectiveness of nebulized fentanyl is an additional benefit. Further studies are warranted to determine the benefit of nebulized fentanyl in decreasing dyspnea symptoms in palliative patients refractory to established treatment modalities.

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**Declaration of competing interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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