FENTANYL FOR RESPIRATORY DISTRESS MANAGEMENT IN HOSPICE SETTINGS

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ABSTRACT: OBJECTIVE: To determine whether fentanyl has greater efficacy compared to morphine for management of respiratory distress in adult patients with terminal illness in hospice settings. METHODS: This nonsystematic literature review considers the efficacy of morphine and fentanyl for relief of dyspnea and respiratory distress. RESULTS: Fentanyl delivers faster onset for relief of symptoms and it offers diverse administrations routes. Additionally, fewer side effects were noted that are commonly associated with opioid medications; these include neurocognitive changes, drowsiness, dizziness, and nausea. CONCLUSIONS: With greater than fifty percent of patients experiencing dyspnea at the end of their life, it is important to address dyspnea and respiratory distress to promote adequate management of these common symptoms. Dyspnea can severely limit the quality of life of individuals with a terminal illness. Although there is evidence to support fentanyl's efficacy in managing dyspnea, more studies are necessary to quantify the significance and potential for this drug compared to other opioid medications.

Introduction

Dyspnea and respiratory distress are common symptoms for patients at the end of life and can severely impact the quality of life in patients with a terminal illness. According to Afolabi, Nahata, and Pai (2017), more than fifty percent of patients will experience dyspnea at the end of their life. The prevalence of episodic breathlessness, dyspnea, and respiratory distress identifies a need in this population for respiratory symptom management. Whether prognosis for life expectancy is limited to days, months, or years there is an immediacy for patients and family to find quality and comfort with end of life care. Life limitations for patients with breathlessness in terms of limiting activity and quality can be significant (Simon et al., 2016). Adult hospice is a setting in which patients can seek end of life symptom management and find a coordinated way to maintain quality of life. While morphine is the drug of choice in many institutions for end of life symptom management, fentanyl has a faster onset compared to morphine and more diverse administration routes.

Respiratory symptom severity and onset can vary widely among patients depending on the illness. Cabezón-Gutiérrez et al. (2016) states, "prevalence of dyspnea varies depending on underlying disease; it ranges from 90 to 95% in chronic obstructive pulmonary disease (COPD), is approximately 78% in lung cancer (LC), ranges from 60 to 88% in congestive heart failure (CHF), and is almost 100% in neuromotor diseases. Dyspnea also causes physical and psychological discomfort, anxiety, and depression" (p. 4045). Anxiety can exacerbate respiratory distress, but proper management at onset of symptoms, regardless of disease, will help alleviate shortness of breath in this population. Opioids are commonly used for end of life symptom management and have proven to be effective for managing pain and dyspnea.

Respiratory symptom management for patients with terminal illness could be improved if the efficacy of fentanyl and morphine are taken into consideration as well as the various administration routes. Consideration for various routes of administration are important for end of life symptom management. Although oral administration continues to be most common and easily accessible, additional research to determine the most appropriate and economic routes for delivery will enhance patient care. Majidinejad, Ebrahimi, Heydari, Ahmadpour, and Esmailian (2019) state, "many patients are unable to take

oral medications. Nebulized morphine provides an alternative route of opioid administration to patients who are unable to use oral medications or those who prefer the convenience of an inhalation medication" (p. 6). Fentanyl and morphine are both available to be nebulized for administration but there are other routes that can be considered for dyspnea relief including oral transmucosal, intravenous, subcutaneous, and transdermal. Intravenous and subcutaneous routes for medication delivery are generally specific to hospitalized patients and are common delivery routes for opioid medications. Outpatients will more likely consider oral transmucosal buccal tablets, nebulized fentanyl, and topical fentanyl (patches). It is important to differentiate hospitalized patients from outpatients (Cabezón-Gutiérrez et al., 2016). This expands the use of these medications to more settings and makes opioid administration increasingly accessible for inpatient and outpatient hospice. After a review of literature, fentanyl has greater efficacy compared to morphine for management of respiratory distress in adult patients with terminal illness in hospice settings.

Review of Literature

Through a review and synthesis of literature, there are important distinctions that were clarified when comparing fentanyl and morphine. Hospice populations deserve special consideration for routes of medication delivery; accessibility to certain routes will depend on inpatient or outpatient settings. Although inpatient and outpatient were not looked at independently of one another for the purposes of this review, fentanyl has multiple modalities for administration that are favorable in comparison to morphine. Studies included were from a search of the following databases: CINHAL, PUBMED, and The Cochrane Library. Five studies were included with a rating of at least 3 or greater on the Level-of-Evidence Hierarchy.

Capper et al. (2010) utilized quantitative methods to study the pharmacokinetics of subcutaneous fentanyl. The population consisted of 9 male volunteers in good health which was determined by their medical history, a physical, and laboratory examination. This study determined that while the rapid absorption rate of subcutaneous fentanyl was similar to subcutaneous morphine, the half-life for fentanyl was substantially longer: ten hours compared to about 2 (Capper et al., 2010). Additionally, blood concentrations do not vary greatly among the two opioid drugs when other routes, except intravenous, were used. The sample size was small for this study, but the controls were well employed. The selection process was not entirely randomized because they were volunteers, but the subjects fit a specific criteria. One volunteer was excluded from the final results for taking an antihistamine which could interrupt results of the pharmacokinetics of fentanyl.

In a systematic review, Simon et al. (2013) regarded fentanyl for the relief of breathlessness. There were 88 patients considered across 622 references and included the following diseases: the majority of patients had lung cancer and chronic obstructive pulmonary disorder (COPD), one patient with interstitial lung disease (ILD), and one patient with cystic fibrosis (CF). The review endorses that fentanyl is promising for providing relief of breathlessness, but more trials are needed to definitively determine this. This systematic review is a valuable study that focuses clearly on the fentanyl use for breathlessness relief, included relevant studies, and was led by experts in breathlessness following high quality methods for conducting a literature search.

Simon et al. (2016) performed a pilot phase II clinical trial involving a randomized, active-control (morphine) to determine the effects of treating episodic breathlessness with transmucosal fentanyl. This trial consisted of adults aged 18 years or older with incurable cancer. The population of the study consisted of 10 individuals on initiation, but only 6 individuals completed the study. Unfortunately, 2 were deceased prior to the conclusion of the study and 2 dropped out due to disease progression. This was a high quality study, . it It was conducted thoroughly for a pilot clinical trial. Ultimately, the study describes relief of episodic breathlessness via transmucosal fentanyl as faster and greater than

morphine and validates further evaluation would be beneficial through a more comprehensive study.

Hui et al. (2019) conducted a parallel, double-blind randomized placebo-controlled trial to determine the efficacy of the prophylactic administration of fentanyl. First, a walking test was performed to determine baseline breathlessness measured by a numerical scale. Then a fentanyl buccal tablet or a placebo was given prophylactically, followed by another walking test to determine efficacy. The population consisted of 20 patients with an active diagnosis of cancer. This study size was small but supported the prophylactic administration of fentanyl. While larger trials are necessary, the conclusion described that fentanyl buccal tablets were associated with a reduction of exertional dyspnea and well tolerated by the participants.

In a retrospective study, Benitez-Rosario, Rosa-González, González-Dávila, and Sanz (2019) analyzed fentanyl for dyspnea relief at the end of life. The population was 72 patients with advanced cancer and non-cancer patients from a Palliative Care Unit that endorsed dyspnea at rest. This study explored intravenous and subcutaneous fentanyl and the data suggests that it does provide relief from dyspnea although it recommends further research to confirm findings.

To summarize, the quality of the body of literature presented here is generally good being sufficiently high on the Level-of-Evidence Hierarchy. Across the studies there is a theme that fentanyl provides relief from dyspnea and breathlessness. Additionally, many of the studies indicate further exploration and trials are warranted to truly explore the potential of fentanyl.

Argument

There are several clinical advantages to fentanyl because it has a faster onset compared to morphine and more diverse administration routes. According to Simon et al. (2013), fentanyl onset takes place within as little as 7 to 16 minutes, while morphine onset is 20 to 30 minutes. Respiratory distress can begin quickly and build as patients feel anxiety from dyspnea and episodic breathlessness. Considering this, it is important for symptom relief to be achieved as quickly as possible. In terms of administration routes, some will inevitably be faster than others, but the diversity of routes make fentanyl a valuable tool for hospice patients. Hospice seeks to accommodate a wide variety of settings and as such, deserves circumstantial consideration for diverse administration routes. Simon et al. (2013) explores diverse routes of fentanyl administration available such as oral transmucosal, intravenous, transdermal, intranasal, and nebulized. Clearly, variety in administration routes in addition to rapid onset, create an important pathway for fentanyl as a primary drug choice for respiratory distress symptom management in the terminally ill. Additionally, subcutaneous fentanyl creates an ease for administration that avoids the need for vascular access or use of complex pumps (Capper et al., 2010). The oral transmucosal method includes the fentanyl buccal tablet which Simon et al. (2016) concluded in 61 episodes of respiratory distress, the fentanyl buccal tablet showed a faster onset of action and helped relief relieve more symptoms than morphine. Symptom management is possible to achieve given the route diversity and fast onset fentanyl offers.

In addition to the clinical advantages described above, fentanyl also has less fewer side effects than morphine because it works directly on breathing and pain receptors. Opioid drugs are powerful analgesics and are used regularly for pain management. Unfortunately, the strong analgesic effects can often be accompanied by unwanted side effects including dizziness, hypotension, neurocognitive changes, respiratory depression, and buildup of the drug due to poor excretion in individuals with organ failure. While morphine and fentanyl are both opioid derived analgesics, there are important distinctions to be made regarding the individual drugs. Afolabi et al. (2017) states, "some institutions may prefer to nebulize fentanyl due to the lack of histamine release and decreased potential for bronchospasm when compared with morphine or hydromorphone" (p.1060). This is especially important deciding appropriate interventions for

respiratory distress. Bronchospasms can further exacerbate respiratory distress which is undesirable given the intention behind the drug administration is to diminish and ease respiratory symptoms. Another study added that there were minimal to no neurocognitive effects which is an important consideration for patients desiring symptom relief without the euphoria and associated high that can accompany opioid drugs (Hui, 2017). Capper et al. (2010) endorses that fentanyl may be safer for certain organ functioning stating, "fentanyl is thought to offer a safer alternative to morphine for patients with renal impairment (because of its lack of renally excreted active metabolites) or for those who are allergic to, or intolerant of, morphine" (p. 241). This could potentially reduce the risk of buildup of the drug leading to respiratory suppression, changes in behavior, and encephalopathy associated with some opioid derivatives. Fentanyl provides less devastation to multiple organ systems in addition to the fewer side effects; the lack of neurological changes is cathartic for many patients and families who welcome lucidity and time with their loved one for as long as possible.

While there may be hesitation adopting the use of fentanyl more commonly from a business position regarding cost and time, it is a fiscally responsible and time conservative option. As far as cost, fentanyl often requires fewer doses to achieve adequate symptom relief which is cost effective when comparing prices on a timeline. This can be partially attributed to some routes, including bolused subcutaneous fentanyl, having a substantial half-life of up to 10 hours (Capper et al., 2010). Additionally, fewer doses improves the time management and efficient workflow for healthcare providers and leads to longer lasting comfort for the patient. Fleischman et al. (2010) affirmed, "the costs of the two drugs are similar, with an average wholesale price of $0.71 for 10 mg of morphine versus $0.83 for 100 μg of fentanyl, our results show no compelling argument for the use of one drug over the other" (p. 173). In light of the minimal cost difference, and fewer doses required to achieve symptom relief, healthcare workflow and patient comfort are improved.

Another potential concern for the wide adoption of fentanyl is from a public health perspective related to overdose deaths, and the stigma that carries. Fentanyl awareness in the public has recently been associated with fear as there are continuous reports of overdose deaths in the media. However, in the hospice setting, fentanyl dosing is regulated and assessed after each administration. In their study, Benitez-Rosario et al. (2019), specified that there were no expedient deaths with the administration of fentanyl for breathlessness as recorded by physicians caring for the patient participants. Cost, timing, and stigma are important considerations but do not outweigh the potential benefits of fentanyl for symptom management in this patient population.

Discussion

Fentanyl is recommended as a primary choice for end of life respiratory distress symptom management when considering its benefits: faster onset, diverse administrations routes, and fewer side effects. Oral routes are commonly used but not always ideal for managing respiratory symptoms. This is especially true because increased oral secretions is an end of life symptom, and while aspiration of the drug may not be concerning at this point, it could increase discomfort of the dying individual. Many hospice settings will not have intravenous access available for medication delivery. Patients, families, and healthcare providers will all appreciate the efficacy and alternative routes fentanyl provides. Protocols by these facilities and individual physician preference may dictate the frequency of fentanyl ordered, but there is evidence that fentanyl may be more effective than morphine (Simon et al., 2016). Previously mentioned, side effects commonly associated with opioid medications can be burdensome. These include neurocognitive changes, drowsiness, dizziness, and nausea. Providing comfort and symptom relief at the end of life is very important and fentanyl is an appropriate alternative to certain options that are commonplace, like morphine. Education on better management for symptoms utilizing medications with fewer side effects are ideal for all stakeholders. The plan of action for recommending fentanyl as

a primary treatment option can be synthesized through Larrabee's Change Model for Evidence-Based Practice. This change model is widely recognized by healthcare providers and can be used to determine appropriate steps when making an evidence-based practice change. Stakeholders are pivotal for practice change and include hospice agencies, healthcare providers, families, and patients.

First, options for disseminating fentanyl will logistically depend on the inpatient or outpatient hospice setting. While intravenous and subcutaneous may be more accessible in inpatient settings, transmucosal buccal tablets and transdermal fentanyl will be exceptionally reliable outpatient alternatives. This will make accessibility easy and provide relief to all end of life sufferers of respiratory distress. Stakeholders will appreciate the interventions as they will provide more consistent relief to their patients and improve workflow. Family and patients will value the prioritization of comfort while they experience a difficult time in their lives.

Next, exploring the literature has guided this recommendation for practice change, to use fentanyl as a first line therapy for respiratory distress and dyspnea relief. It may be difficult to convince all stakeholders, but with more use in practice, fentanyl's efficacy will be more readily apparent and accepted as a positive, evidence-based practice change. This change in practice is feasible in hospice settings because current evidence maintains fentanyl as a great alternative to morphine due to the multiple modalities available for administration and the fewer instances of side effects.

Practice change is best achieved when all stakeholders are working towards a common goal and are effectively informed. Education will be necessary to indicate the usefulness of fentanyl for better respiratory distress symptom management. This will include advocacy for individual patient conditions with the most ideal delivery and absorption for individual patients. Evaluating the effectiveness of implementing fentanyl will be slightly different whether the hospice setting is inpatient or outpatient. Chart auditing for symptoms prior to medication administration and reassessment for effectiveness of symptom relief will be a reliable measurement tool. Gathering surveyed data from healthcare providers on how well patients tolerate the medication change will also indicate its efficacy. Suggestions from stakeholders for improvement are always valuable and welcomed.

Conclusion

Compared to morphine, fentanyl has greater efficacy for management of respiratory distress in adult patients with terminal illness in hospice settings. Fentanyl is a reliable treatment for dyspnea and respiratory distress in patients who are terminally ill. With its range of routes, fewer side effects, and quicker onset, fentanyl is superior to morphine for end of life symptom management and can be widely applied in inpatient and outpatient hospice settings. More studies are necessary to quantify the significance and potential for fentanyl, but the recommendation is that fentanyl should be a first choice intervention.

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