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CASE REPORT

Intensive symptom control of opioid-refractory dyspnea in congestive heart failure: Role of milrinone in the palliative care unit

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ABSTRACT

Objective: We describe an exemplary case of congestive heart failure (CHF) symptoms controlled with milrinone. We also analyze the benefits and risks of milrinone administration in an unmonitored setting.

Method: We describe the case of a patient with refractory leukemia and end-stage CHF who developed severe dyspnea after discontinuation of milrinone. At that point, despite starting opioids, she had been severely dyspneic and anxious, requiring admission to the palliative care unit (PCU) for symptom control. After negotiation with hospital administrators, milrinone was administered in an unmonitored setting such as the PCU. A multidisciplinary team approach was also provided.

Results: Milrinone produced a dramatic improvement in the patient's symptom scores and performance status. The patient was eventually discharged to home hospice on a milrinone infusion with excellent symptom control.

Significance of Results: This case suggests that milrinone may be of benefit for short-term inpatient administration for dyspnea management, even in unmonitored settings and consequently during hospice in do-not-resuscitate (DNR) patients. This strategy may reduce costs and readmissions to the hospital related to end-stage CHF.

KEYWORDS: Congestive heart failure, Opioid-refractory dyspnea, Palliative care, Milrinone

INTRODUCTION

Congestive heart failure (CHF) is an emerging epidemic that affected approximately 6.6 million Americans in 2010 and is projected to affect 10 million by 2030 (Heidenreich et al., 2011). CHF accounted for 1.2–1.3 million U.S. hospitalizations in 2004 (Go et al., 2013), mostly due to dyspnea. A distressing symptom, dyspnea presents in about 60–88% of patients with CHF (Solano et al., 2006) and is associated with declining functional status (Laoutaris et al., 2004), poor quality of life (Karapolat et al., 2008; Caraceni, 2012) and loss of will to live (Chochinov et al., 2005). Dyspnea also has profound effects on patients with chronic obstructive pulmonary disease (Hajiro et al., 1999; Holm et al., 2009) or cancer (Gupta et al., 2007).

Opioids are the cornerstone of symptom management in dyspnea (Parshall et al., 2012), though they are not universally efficacious (Currow et al., 2007). In fact, management of refractory dyspnea in

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advanced illness is still one of the most challenging tasks across medical specialties (Parshall et al., 2012). Inotropes such as milrinone may be required for patients with CHF refractory to opioids (Felker & O'Connor, 2001).

Milrinone is a phosphodiesterase-3 (PDE-3) inhibitor with inotropic, lusitropic (promoting diastolic relaxation), and vasodilator effects (Honerjager, 1991). Upon PDE inhibition, cyclic AMP levels increase, which consequently increases the level of intracellular calcium and cardiac contractility and hence the cardiac index (Honerjager, 1991; Majure & Teerlink, 2011; Milfred-LaForest et al., 1999). However, the effects of PDE inhibition on heart rate or blood pressure are negligible. Milrinone is particularly effective for patients with end-stage heart failure (ESHF) (Cesario et al., 1998), where symptom management is compulsory. However, toxicities related to milrinone use—such as hypotension (Cesario et al., 1998), fatal arrhythmia (Holmes et al., 1985), and tachyphylaxis (Cesario et al., 1998; Packer et al., 1991; Honerjager, 1991)—and its potential for inducing death restrict its use to highly complex and monitored settings, such as intensive care units (ICUs). Because a palliative care unit (PCU) generally does not have monitors and due to strict hospital policies, gaining approval to administer inotropes in that setting may prove to be challenging. Opioids have no known interaction with milrinone, so they might be used in combination efficaciously.

We describe dramatic improvement in opioid-refractory dyspnea obtained using milrinone in an ESHF patient with leukemia who had been admitted to our PCU. She was subsequently transferred to hospice care and was able to maintain good symptom control with milrinone. Success in this case resulted in a major policy shift at our hospital regarding unmonitored use of milrinone and similar cardiac agents for symptom relief of dyspnea in do-not-resuscitate (DNR) patients on the PCU.

CASE DESCRIPTION

Mrs. M (the patient's name was changed in the interests of confidentiality) was a 57-year-old Caucasian female with a medical history of breast cancer who had been treated with chemotherapy, surgery, and radiotherapy 10 years prior to her most recent presentation at our treatment center. She had been treated with several lines of chemotherapy over the course of five years after having initially having been diagnosed with acute promyelocytic leukemia and later myelodysplastic syndrome, which had progressed to an acute myeloid leukemia that was refractory to treatment. The patient's comorbidities had included CHF secondary to chemotherapy-associated cardiomyopathy and diabetes mellitus. Dyspnea on exertion had progressed during the three years prior to her last admission, at which time she had presented with dyspnea at rest (class 4 New York Heart Association [NYHA] functional classification). The most recent echocardiogram had revealed a left-ventricular ejection fraction of 20–25% with global hypokinesis, moderate dilation, moderate to severe tricuspid regurgitation, and an elevated right-ventricular systolic pressure of 40–50 mm Hg.

Before her last admission, Mrs. M had presented three times in the previous three months for hypotension and CHF exacerbation. One of these presentations had required admission to the ICU. During her stay there, cardiology had recommended an intravenous milrinone drip for symptom control in view of the presence of hypotension and the refractoriness of the dyspnea. Administration of milrinone had improved the patient's symptoms, and she had been able to tolerate diuretic agents, beta blockers, and angiotensin-converting enzyme inhibitors. The patient was eventually discharged home with home healthcare on milrinone drip and oral medications.

However, the morning after discharge, she was admitted back into the hospital complaining of fever. She also had experienced anxiety and dyspnea. On arrival to the emergency center (day 1), her blood pressure was 85/48 mm Hg, her heart rate was 133 bpm, her respiratory rate 26 breaths per minute, and oxygen saturation 89% on room air. Mrs. M's lungs were clear to auscultation and percussion. Auscultation of the heart revealed tachycardia with regular rhythm and a systolic ejection murmur. The patient's lower extremities showed bilateral +2 pedal edema. Her Eastern Cooperative Oncology Group performance status score was 4. Her blood counts were unremarkable except for positive blasts on the peripheral blood smear. The chest x-ray was negative for infiltrates.

Because the leukemia was refractory, Mrs. M and her husband had a prolonged encounter with the medical team in which it was explained that she was not eligible for further therapy. The palliative medicine team assisted in communicating palliative care interventions such as symptom control with morphine and discontinuation of milrinone. The patient opted for a DNR order and agreed to be transferred to the PCU to facilitate end-of-life discussions and eventual transfer to hospice care. This discussion generated significant anxiety for Mrs. M, so the medical team provided expressive supportive counseling. She was also started on broad-spectrum antibiotics in view of a suspicion of sepsis.

On day 2, the patient's dyspnea was still exacerbated significantly despite treatment with opioids at 60 mg of morphine equivalent daily dose (MEDD).

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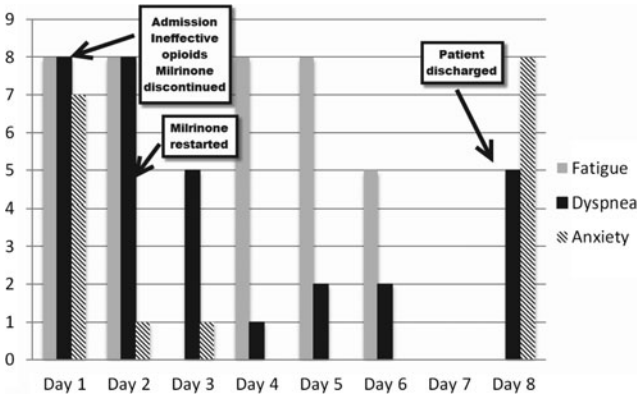

Fig. 1. Edmonton Symptom Assessment System (ESAS) scores for patient. Scale ranges from 0 (no symptoms) to 10 (worst symptom ever). The patient was admitted to the hospital on day 1 and discharged to at-home hospice care on day 8.

Because of her hypotension, the morphine dose could not be increased. The physical examination revealed bilateral crackles, which was compatible with pulmonary edema. At that point, cardiology was consulted emergently, and they suggested that a milrinone drip be restarted. Intensive discussions were carried out with the hospital's pharmaceutics and therapeutics committee to allow for administration of milrinone in an unmonitored setting (i.e., the PCU) for purposes of symptom relief. After approval by the scientific director of the hospital, Mrs. M received milrinone at the PCU without telemetry at 0.5 μg/kg/hour. After this multidisciplinary team approach, her Edmonton Symptom Assessment System (ESAS) score for anxiety decreased from 7 (on day 1) to 1 (on day 2) (see Figure 1).

On day 4 (within 48 hours after milrinone was restarted), the patient's ESAS score for dyspnea had dropped from 8 to 1. The score for fatigue had also dropped, from 8 on day 1 to 0 on day 3. Her MEDD remained fairly stable during the rest of her PCU stay (see Table 1). Because the results of her blood and urine cultures were negative, the fever etiology was thought to be related to the leukemia, so antibiotic treatment was discontinued.

During Mrs. M's 8-day PCU stay, her daily diuretic treatment with furosemide and spironolactone was adjusted satisfactorily with an acceptable fluid balance, and beta blockers were restarted. On discharge from the PCU, the patient's functional status improved dramatically. She went from being completely bedridden with dyspnea at rest to being able to ambulate with a walker, eat without discomfort, and pursue activities of daily living (bathing, brushing her hair, and getting dressed). Emotionally, Mrs. M stated that she felt very peaceful and was looking forward to spending the rest of her life at home. There were some issues with mild anxiety prior to discharge due to the uncertainty of her symptom management at home, but this was satisfactorily addressed by our psychosocial team.

In view of the proven refractoriness of this patient's dyspnea to opioids and best medical management, her insurance company agreed to pay for both hospice care and milrinone. She was able to remain at home and, according to a subsequent phone interview, had minimal discomfort. Surrounded by her family and hospice care team, she passed away 22 days after discharge.

COMMENT

Congestive heart failure is the most common cause of hospital admission and readmission among Medicare beneficiaries (Jencks et al., 2009). Given CHF's epidemic proportions and the associated morbidity and mortality, evidence-based palliative care interventions to reduce both the suffering of and medical costs to patients are required, especially at the end of life. Although the use of aggressive interventions is not usual in palliative or hospice care, the case we present highlights three potential benefits of aggressive management of symptoms with the use of milrinone in ESHF, because of its pharmacologic action reviewed elsewhere (Benotti et al., 1985).

First, our patient experienced a dramatic improvement in dyspnea shortly after milrinone was

Table 1. *Morphine equivalent daily dose (MEDD) and diuretic doses during patient's hospital stay*

Hospital Day	MEDD	Furosemide Daily Dose	Spironolactone Daily Dose	Comments
1	36	Held due to hypotension	Held due to hypotension	Patient admitted
2	60	Held due to hypotension	Held due to hypotension	Milrinone restarted
3	50	20 mg I.V. in a.m.	50 mg P.O. in a.m.	
4	55	"	"	
5	54	40 mg I.V. in a.m.	"	
6	57	"	100 mg P.O. in a.m.	Patient anxious about family meeting
7	51	"	"	
8	63	"	"	Patient discharged; patient anxious

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reinitiated. In cases of opioid-resistant dyspnea, milrinone, which directly stimulates cardiac contractility without increasing myocardial oxygen consumption (Charisopoulou et al., 2014), may be required to control dyspnea. The remarkable response induced by milrinone in our patient resulted in an institutional policy change: all patients with a DNR order on file and refractory symptoms related to ESHF may now receive inotropes in the PCU. Monitoring of milrinone blood levels has been advocated as a surrogate for telemetric monitoring (Vazir et al., 2011), but it is largely unpractical at the end of life, when only comfort measures are warranted. In cases of opioid-resistant dyspnea, symptom management is one of the compelling reasons to continue administering inotropes in the palliative care setting. Failure to do so will result in inappropriate rapid uptitration of opioids and the risk of delirium (Oosten et al., 2011), and it may unnecessarily increase an early need for palliative sedation to control intractable dyspnea or delirium (Caraceni et al., 2012; Mercadante et al., 2009). A DNR order should not prevent consultation with cardiology and other staff, who are making all efforts to provide maximal medical therapy.

Second, some clinicians might have argued against the need for admitting our patient to the PCU. However, given the high anxiety she experienced after discussion of her prognosis and the additional discussions that occurred about DNR status in the emergency department, it was determined that the PCU was, at that time, the best setting in which to care for this patient, who was now near the end of her life. A team of medical experts in symptom control and a highly skilled psychosocial team were assets in managing the patient's discomfort. In the PCU and under sufficient nurse supervision, our patient received milrinone infusion and, subsequently at home in a completely unmonitored setting. However, almost all hospitals will insist on a telemetry monitor when inotropes are provided. Such a policy is untenable compared with the use of midazolam and propofol without monitoring for palliative sedation in the PCU. For the patient and her husband, the intervention of a multidisciplinary team and best medical therapy were reassuring. As a result, our patient felt peaceful and was able to address issues that were important to her and her family.

Third, cost-containment strategies could well use inotropes in its armamentarium for short-team symptom management in CHF. The direct and indirect medical costs for CHF in 2010 were $34.4 billion, and these numbers are expected to triple by 2030 (Heidenreich et al., 2011). The mean cost of a CHF-related hospitalization was $18,000–$23,000 per patient in 2008 (Titler et al., 2008), which is a rapid escalation from the $10,000 calculated for 1991 (O'Connell & Bristow, 1994; Honerjager, 1991; Jencks, 2009). The care of NYHA class 4 heart failure patients, including outpatient care, is the most expensive compared to classes 1, 2, or 3 (Malek, 1999), considering that more ICU admissions occur near the end of life. The patient's total expenditure for her last 11-day ICU admission alone was more than $100,000, while her 10-day PCU admission cost was $42,000. Furthermore, current government policies penalize hospitals for CHF readmissions within 30 days, but the rate of these readmissions has been estimated to be as high as 27% (Jencks et al., 2009). We propose that providing intermittent inotropic infusions with milrinone for outpatients (in a hospice setting) is a cost-effective alternative. The cost of milrinone for our patient was $7 per day, with a daily range of $7–50 (Majure & Teerlink, 2011). A simple cost analysis proves that the use of milrinone is financially advantageous for ESHF patients and thus for the healthcare system. In addition, the use of inotropes may reduce readmissions and decrease hospital stays by about 80% for patients with NYHA class 3 or 4 illness (Marius-Nunez et al., 1996).

We are aware that inotropic infusions may not be covered by Medicare and that CHF patients may forsake hospice enrollment because they believe their health insurance will not cover the use of inotropes. This reasoning, which is prevalent, may explain why only 2.5–20% of CHF patients receive hospice benefits (Whellan et al., 2012). In the case of Mrs. M, coverage for both hospice and intravenous milrinone was negotiated with the patient's private insurance, which abrogated the need for hospital readmission. This case suggests that such an arrangement is feasible for ESHF patients as a cost-containment strategy, even with Medicare/Medicaid patients.

In conclusion, we strongly advocate the unmonitored use of all medications that provide comfort to patients at the end of life when being treated in a PCU setting. Patients for whom no other conventional therapies against dyspnea are available might be willing to accept the greater risk of death associated with the proarrhythmic effects of intravenous inotropes (Packer et al., 1991) in exchange for some symptom relief. With our patient Mrs. M, good symptom control was achieved not only by us while she was admitted to the hospital but also in the outpatient setting due to arrangements made between hospice care and her insurance carrier.

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