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Use of oral hydromorphone in a patient with stage D heart failure

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Abstract

Patients with advanced heart failure often experience dyspnea, fatigue, edema, and appetite loss. If these symptoms are refractory to treatment, palliative care via a team approach is necessary. We describe a patient with stage D heart failure whose dyspnea and overall condition improved with comprehensive medical treatments including conventional medications for heart failure, continuous infusions of catecholamine and diuretic, and oral hydromorphone. A 67-year-old man with a 12-year history of dilated cardiomyopathy was admitted to our hospital due to exacerbation of heart failure. Despite continuous infusion of catecholamine and diuretic, his dyspnea and liver and renal function continued to worsen. Oral hydromorphone was administered to relieve his refractory dyspnea, which also improved his conditions, continuous infusion of the catecholamine and diuretic could withdraw. Oral low-dose hydromorphone used in the present case might be a helpful agent for treating dyspnea in stage D heart failure patients with renal dysfunction.

Keywords

Palliative care, heart failure, hydromorphone

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Introduction

Chronic heart failure (HF) is a serious condition associated with high morbidity and mortality rates.[1] Stage D patients are defined as,

> patients with truly refractory HF who might be eligible for specialized, advanced treatment strategies, such as mechanical circulatory support, procedures to facilitate fluid removal, continuous inotropic infusions, cardiac transplantation, other innovative or experimental surgical procedures, or for end-of-life care such as hospice.[2]

In patients with stage D HF, palliative care should be provided alongside advanced treatment strategies; recognition of the need for palliative care for HF patients, however, is less prevalent than for patients with malignancies.[3] Barriers disrupting the provision of palliative care to patients with advanced HF include the condition's unpredictability, recurrent exacerbations, difficulties anticipating the condition's terminal phase, and lack of an established medical treatment regimen that includes opioids.[3] We report a case of stage D HF in which the patient's symptoms of dyspnea, malaise, and insomnia were alleviated by oral hydromorphone.

Case report

A 55-year-old man was diagnosed with dilated cardiomyopathy and treated with optimal pharmacological therapy, including an angiotensin-converting enzyme inhibitor, a β-blocker, furosemide, and spironolactone. At age 62 years, a cardiac resynchronization therapy defibrillator (CRT-D) and tolvaptan were introduced for worsening HF and complete left bundle branch block. Despite optimal medical therapies, he was admitted to our hospital three times between the ages of 65 and 66 years due to HF exacerbations, and multidisciplinary interventions by doctors, nurses, pharmacists, nutritionists, and physiotherapists were initiated. During this

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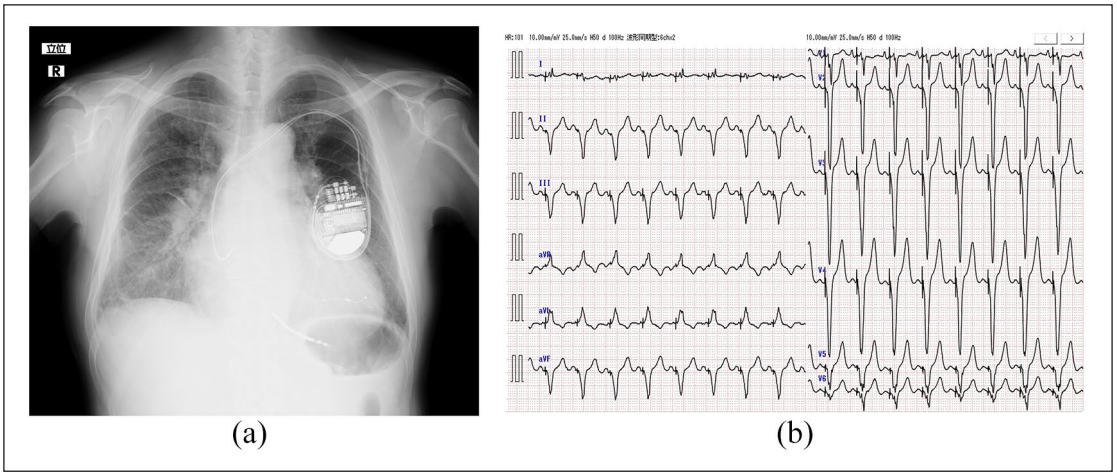

Figure 1. A chest X-ray on admission revealed significant cardiomegaly with pulmonary congestion and an implanted CRT-D (a) and a 12-lead ECG revealed sinus tachycardia with all biventricular pacing (b).

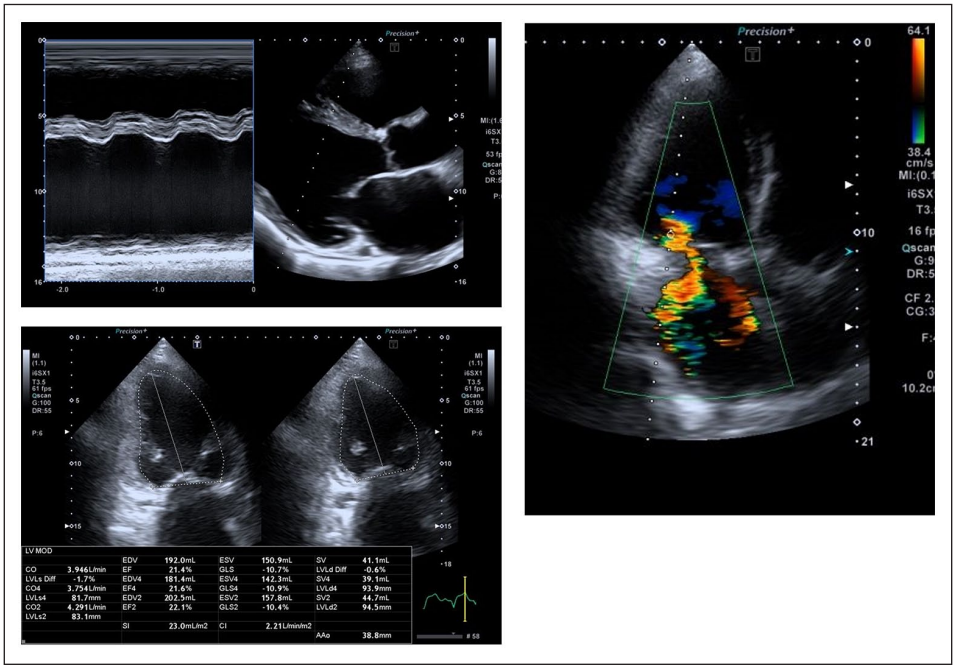

Figure 2. A transthoracic echocardiogram on admission revealed severe left ventricular dysfunction with marked dilatation of the chambers and severe functional mitral regurgitation.

period, we repeatedly recommended transcatheter mitral valve repair for severe functional regurgitation, but he declined. Adaptive servo-ventilation was introduced to relieve dyspnea, but rather was discontinued due to the discomfort caused by wearing the device. A month after discharge, his HF symptoms of dyspnea at rest, malaise, insomnia, and appetite loss recurred, and a fourth hospitalization was required.

Physical examination revealed lip cyanosis, jugular venous distention, liver swelling, bilateral leg edema, and a systolic murmur with the Levine scale grade of III/VI at the apex. His blood pressure was 82/68 mm Hg, his heart rate was 102 bpm and regular, his respiratory rate was 24/min, and his peripheral oxygen saturation was 96% on room air. A chest X-ray on admission revealed significant cardiomegaly with pulmonary congestion (Figure 1(a)). A 12-lead electrocardiogram (ECG) revealed sinus tachycardia with biventricular pacing, which was unchanged compared to the previous findings (Figure 1(b)). A transthoracic echocardiogram revealed severe left ventricular dysfunction with a reduced ejection fraction of 21% and marked dilatation of the chambers (left ventricular end-diastolic diameter of 72 mm and left atrium diameter of 61 mm). Severe functional mitral regurgitation, with an effective regurgitant orifice of 0.62 cm^2, was also observed (Figure 2). Laboratory studies revealed a brain natriuretic peptide level of 864 pg/mL,

Table 1. Laboratory data on admission.

WBC (cells/μL)	4.5×10^3	LDH (U/L)	287	Cl (mEq/L)	94
Hb (g/dL)	13.0	ALP (U/L)	278	BS (mg/dL)	216
Ht (%)	37.6	γ-GTP (U/L)	48	HbA1c (%)	7.7
MCV (fL)	88.9	T-bil (mg/dL)	0.8	BNP (pg/mL)	864
MCHC (%)	34.6	CK (U/L)	112	CRP (mg/dL)	0.56
Platelets (/μL)	22.9×10^4	BUN (mg/dL)	33.1		
		Cre (mg/dL)	1.45		
Alb (g/dL)	3.4	UA (mg/dL)	7.7		
AST (U/L)	48	Na (mEq/L)	130		
ALT (U/L)	39	K (mEq/L)	4.3		

WBC: white blood cell; Hb: hemoglobin; Ht: hematocrit; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; Alb: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; γ-GTP: γ-glutamyl transpeptidase; T-bil: total bilirubin; CK: creatinine kinase; BUN: blood urea nitrogen; Cre: creatinine; UA: uremic acid; Na: sodium; K: potassium; Cl: chlorine; BS: blood sugar; HbA1c: hemoglobin A1c; BNP: brain natriuretic peptide; CRP: C-reactive protein.

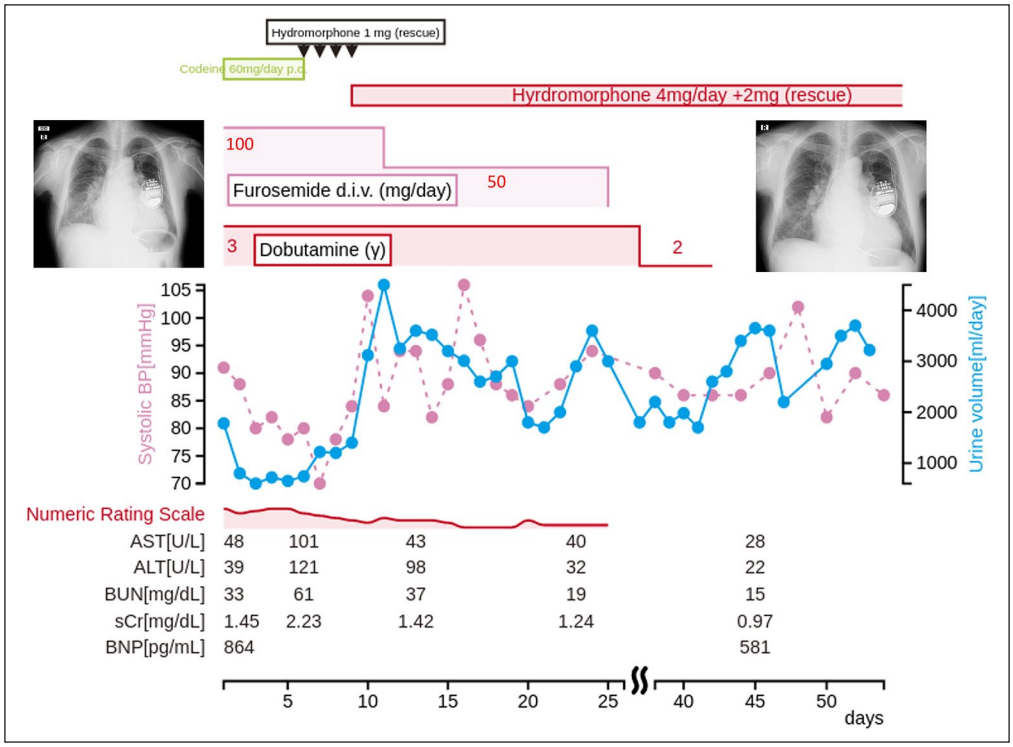

Figure 3. The clinical course during hospitalization.
AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; sCr: serum creatinine; BNP: brain natriuretic peptide.

deterioration of renal function, a blood urea nitrogen level of 33.1 mg/dL, and a serum creatinine level of 1.45 mg/dL (Table 1).

The clinical course during hospitalization was shown in Figure 3. We initiated a continuous infusion of dobutamine 3γ and furosemide 100 mg/day based on a diagnosis of an HF exacerbation complicated by organ dysfunction. In addition, his oral pre-hospitalization medications were continued, including enalapril 2.5 mg, carvedilol 5 mg, tolvaptan 15 mg, furosemide 40 mg, spironolactone 25 mg, and empagliflozin 10 mg. Despite continuous infusion of dobutamine and furosemide, laboratory data 3 days after admission revealed worsening organ dysfunction (aspartate aminotransferase level of 101 U/L, alanine aminotransferase level of 121 U/L, blood urea nitrogen level of 61 mg/dL, and serum creatinine level of 2.23 mg/dL). Furthermore, his respiratory rate increased, and shortness of breath during conversation was observed. With informed consent from the patient and his family, we decided to initiate oral opioids, which had been approved by the internal ethics committee.

We first prescribed oral codeine phosphate hydrate 60 mg/day, but this failed to relieve his symptoms. We then switched

to oral immediate-release hydromorphone 1 mg. Since he often experienced dyspnea after meals as well as insomnia, hydromorphone was regularly administered as a prophylactic before meals and at bedtime. In dose titration, oral extended-release hydromorphone 4 mg once daily and oral immediate-release hydromorphone 2 mg as rescue administration relieved his symptoms and improved his ability to perform activities. No side effects were observed after opioid administration, his systolic blood pressure was approximately 80–100 mm Hg, his heart rate was approximately 90 bpm, his respiratory rate was less than 20/min, and excessive respiratory depression was not induced. In addition to symptom alleviation, his urine volume increased, and his general condition and blood examination findings gradually improved. Introducing cardiac rehabilitation by physiotherapists and foot bath therapy we previously reported, furosemide infusion was withdrawn on hospital day 25, and dobutamine was withdrawn on hospital day 42. Treatment with HF medications and oral extended-release hydromorphone was continued, and he was discharged to home on hospital day 54. After discharge, he continued to take hydromorphone in addition to optimal medical treatment, and received continuous infusions of dobutamine and furosemide three times a week at an outpatient clinic.

Discussion

HF is a complex clinical syndrome that results from any structural and/or functional impairment of ventricular filling or ejection of blood and leads to dyspnea, fatigue, edema, and limited exercise tolerance, and is a serious condition with high morbidity and mortality rates.[1,2] According to World Health Organization (WHO)[4] definition of palliative care, through early identification and impeccable assessment and treatment of pain and other physical, psychosocial, and spiritual problems, palliative care improves the quality of life of patients and their families by preventing and relieving suffering in patients who are facing problems associated with life-threatening illnesses. Although the symptoms and prognosis of stage D HF are recognized as equivalent to those of untreatable cancer, palliative care for stage D HF patients has not been fully accepted in clinical practice in the past.[3] In recent years, based on accumulated evidence, each guideline recommends palliative and end-of-life care.[1,2,5] In aging societies, especially in Asian countries, the prevalence and mortality of HF have increased, and the need for palliative and end-of-life care for elderly patients with advanced HF is currently recognized.[6,7] According to the results of a nationwide survey in Japan, the majority of institutions recognized the necessity of palliative care for HF patients, and two-thirds of institutions prescribed analgesics and/or sedatives as palliative care, with intravenous morphine being most commonly, and oral opioids were limited.[8]

There are specific challenges in managing the symptoms of stage D HF patients. Almost 90% of advanced HF patients have been reported to experience dyspnea with minimal exertion or at rest, which substantially limits their ability to perform daily activities. Oxygen therapy can relieve dyspnea in hypoxemic patients, but its efficacy for patients with mild hypoxemia or normoxia is still uncertain.[9] Noninvasive positive pressure ventilation including adaptive servo-ventilation, rather than standard oxygen alone, may relieve dyspnea and improve hemodynamic status in patients with acute decompensated HF,[10] although it could not be introduced due to the discomfort caused by wearing the device. Opioids are the main pharmacotherapy for dyspnea. The mechanisms by which opioids relieve dyspnea include decreasing respiratory rate, reducing tidal volume, decreasing the central perception of dyspnea, altering peripheral opioid receptor activity in the respiratory tract, and decreasing anxiety. Current guideline recommends low-dose, sustained-release oral morphine for refractory dyspnea,[5] but clinical studies have failed to establish the short- and long-term efficacy of oral morphine for HF patients.[11,12]

In Japan, the oral opioids available for patients with cancer include codeine, morphine, oxycodone, and hydromorphone. Morphine is metabolized to morphine-3-glucuronide and morphine-6-glucuronide by the liver, and these metabolites are excreted by the kidneys. Morphine-6-glucuronide is more pharmacologically active than morphine itself; therefore, morphine could be difficult to use for advanced HF patients with severe renal dysfunction. Oxycodone is a semi-synthetic opioid that is indicated for moderate to severe pain, but its use for dyspnea is off-label. Tanaka et al.[13] have reported a case in which oxycodone was effective for treating dyspnea in a patient with end-stage HF and renal insufficiency. They have also suggested that palliative care treatment of dyspnea is important in the management of HF patients in the terminal stage, as dyspnea can stimulate the sympathetic nervous system, which can exacerbate the condition and lead to medically refractory HF.

Hydromorphone is also a semi-synthetic opioid that has recently become available in Japan as an analgesic for moderate to severe pain caused by cancer. Hydromorphone can be initiated at a low dose, and in extended-release form, its effect can be maintained when taken once a day. Unlike other opioids such as oxycodone and codeine, hydromorphone is not metabolized by the cytochrome P-450 enzyme pathway, thus reducing the potential for significant drug–drug interactions. This drug is metabolized by glucuronidation of the liver into hydromorphone-3-glucuronide, and excreted by the kidneys. Accumulation of this metabolite may cause neurotoxic effects in patients with renal dysfunction.[14] Although oral administration of low-dose hydromorphone is preferred for elderly patients with HF and/or renal dysfunction,[15,16] evidence on its safety and efficacy is lacking. Opioid treatment requires attention to potential side effects including hypotension, excessive respiratory depression, overdose risk, and depressed consciousness, and we were able to avoid these side effects using oral low-dose hydromorphone in the present case.

Palliative care with comprehensive team intervention is important, as is pharmacotherapy. In addition to appropriate

medical treatment, assessments and interventions regarding life environment, social background, nutrition, physical activity, and psychology are needed. In the present case, oral low-dose hydromorphone might be a helpful agent for treating dyspnea in stage D HF patients with renal dysfunction. We hope that opioid therapy will be safe and effective for symptomatic relief in the palliative care of stage D HF patients.

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Declaration of conflicting interests

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Ethical approval

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Informed consent

Written informed consent was obtained from the patient for his anonymized information to be published in this article.

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References

1. Ponikowski P, Voors AA, Anker SD, et al.; ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129–2200.
2. Writing Committee Members; Yancy CW, Jessup M, Bozkurt B, et al.; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; 128: e240–e327.
3. Jaarsma T, Beattie JM, Ryder M, et al.; Advanced Heart Failure Study Group of the HFA of the ESC. Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2009; 11(5): 433–443.
4. World Health Organization (WHO). *WHO definition of palliative care*. Geneva: WHO, 2020.
5. Tsutsui H, Isobe M, Ito H, et al. JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure. *Circ J* 2019; 83: 2084–2184.
6. Shimokawa H, Miura M, Nochioka K, et al. Heart failure as a general pandemic in Asia. *Eur J Heart Fail* 2015; 17(9): 884–892.
7. Okumura T, Sawamura A and Murohara T. Palliative and end-of-life care for heart failure patients in an aging society. *Korean J Intern Med* 2018; 33(6): 1039–1049.
8. Kuragaichi T, Kurozumi Y, Ohishi S, et al. Nationwide survey of palliative care for patients with heart failure in Japan. *Circ J* 2018; 82: 1336–1343.
9. Clark AL, Johnson M, Fairhurst C, et al. Does home oxygen therapy (HOT) in addition to standard care reduce disease severity and improve symptoms in people with chronic heart failure? A randomised trial of home oxygen therapy for patients with chronic heart failure. *Health Technol Assess* 2015; 19(75): 1–120.
10. Nakano S, Kasai T, Tanno J, et al. The effect of adaptive servo-ventilation on dyspnoea, haemodynamic parameters and plasma catecholamine concentrations in acute cardiogenic pulmonary oedema. *Eur Heart J Acute Cardiovasc Care* 2015; 4(4): 305–315.
11. Oxberry SG, Torgerson DJ, Bland JM, et al. Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial. *Eur J Heart Fail* 2011; 13(9): 1006–1012.
12. Johnson MJ, Cockayne S, Currow DC, et al. Oral modified release morphine for breathlessness in chronic heart failure: a randomized placebo-controlled trial. *ESC Heart Fail* 2019; 6(6): 1149–1160.
13. Tanaka M, Maeba H, Senoo T, et al. Efficacy of oxycodone for dyspnea in end-stage heart failure with renal insufficiency. *Intern Med* 2018; 57: 53–57.
14. Lee KA, Ganta N, Horton JR, et al. Evidence for neurotoxicity due to morphine or hydromorphone use in renal impairment: a systematic review. *J Palliat Med* 2016; 19(11): 1179–1187.
15. Černíček V, Gřiva M, Hegmonová E, et al. Opioids for the treatment of dyspnoea in patients with chronic heart failure. *Cor Vasa* 2018; 60: e89–e93.
16. Owsiany MT, Hawley CE, Triantafylidis LK, et al. Opioid management in older adults with chronic kidney disease: a review. *Am J Med* 2019; 132(12): 1386–1393.