**Efficacy of Oxycodone for Dyspnea in End-stage Heart Failure with Renal Insufficiency: A Case Report**

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**Abstract:**
A 67-year-old man with dilated cardiomyopathy and renal insufficiency was admitted to our hospital with dyspnea secondary to end-stage heart failure. We introduced oxycodone for medically refractory dyspnea instead of morphine because of the patient’s renal insufficiency. After the administration of oxycodone, his dyspnea was alleviated without any adverse opioid effects, such as respiratory depression. After treating his heart failure, he was able to leave the intensive care unit. Oxycodone may therefore be a reliable agent for the treatment of dyspnea in patients with end-stage heart failure and renal insufficiency.

**Key words:** dyspnea, terminal-stage heart failure, oxycodone

**Introduction**
Patients with advanced heart failure often experience symptoms including pain, weakness, fatigue, nausea, anorexia, constipation, edema, cough, altered mental status, anxiety, depression, and sleep disorders (1, 2). Most patients with end-stage heart failure complain of dyspnea (2), and in this population, this symptom may be worse compared to that experienced by patients with other advanced illnesses (3). Following reports demonstrating the efficacy of opioids for dyspnea in cancer patients, the current evidence-based practice is to treat dyspneic cancer patients with opioids (4). For example, systemic morphine administration has been reported to be an effective pharmacological treatment to control dyspnea in patients with advanced cancer. A Cochrane review and meta-analysis of the use of opioids for dyspnea noted a small but statistically significant improvement in breathlessness severity with oral opioids versus placebo (5). While consensus has been achieved for the management of dyspnea in patients with terminal cancer, the optimal management of dyspnea in patients with end-stage heart failure has not yet been determined, although some studies report that morphine is beneficial in these cases (6).

We herein present the case of a dyspneic patient with end-stage heart failure and renal dysfunction who was effectively treated with oxycodone. We evaluated the efficacy of opioid treatment using the Modified Borg Scale, an instrument that quantifies dyspnea symptoms on a scale from 0 (no symptoms) to 10 (worst possible symptoms). The Modified Borg Scale enables an assessment of the respiratory discomfort perceived by the patient [(7), (Table)].

**Case Report**
In July 2014, a 67-year-old man with dyspnea was admitted to our department. He had been diagnosed with dilated cardiomyopathy at 56 years of age at another hospital. His past medical history was significant for paroxysmal atrial fibrillation, severe functional mitral regurgitation, chronic kidney disease, and sleep apnea syndrome. We had admitted the patient five times before because of worsening symptoms of heart failure despite optimal medical treatment including a beta blocker and spironolactone. He had also been receiving an angiotensin-converting enzyme inhibitor, but this was discontinued before the latest admission because it had caused symptomatic hypotension. We had implanted a cardiac resynchronization therapy defibrillator for his medi-

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cally refractory heart failure one month prior to this presentation, namely during his fifth admission. At that time, we judged that cardiac resynchronization therapy might allow the patient to avoid hospitalization due to a worsening heart failure and improve his prognosis by correcting his dyssynchrony, and thus leading to an expected reduction of mitral regurgitation. The patient’s level of consciousness on the sixth admission was normal, but the physical examination showed distended neck veins and bilateral leg edema. Cardiac auscultation revealed weak heart sounds with a Levine scale grade 3 pansystolic murmur heard maximally at the apex. Auscultation of the lungs revealed no inspiratory rales. The patient’s heart rate was 88 beats/min and regular, and his arterial blood pressure was 77/55 mmHg. A chest X-ray revealed cardiomegaly with mild pulmonary congestion and no pleural effusion (Fig. 1). A 12-lead electrocardiogram showed all pacing rhythm without newly developed ST-T changes compared with his previous electrocardiogram (Fig. 2).

The transthoracic echocardiography study demonstrated diffuse, severe left ventricular dysfunction with an ejection fraction of 26% estimated by the modified Simpson’s method and a severely dilated left atrium. Moreover, we observed severe functional mitral regurgitation due to the poor coaptation of the mitral leaflet in the patient’s severely dilated left ventricle. His left atrial dimension, volume, and volume index were 59 ml, 110 ml, and 61 ml/m² respectively. His ventricular diastolic dimension was 87 mm, and the effective regurgitant orifice calculated by the proximal isovelocity hemispheric surface area method was 0.79 cm² (Fig. 3).

On admission, the patient’s N-terminal pro-brain natriuretic peptide was markedly elevated (15,943 pg/dL; normal range, <125 pg/mL), and his creatinine was 2.27 mg/dL. We diagnosed acute decompensated heart failure based on the worsening of his chronic heart failure symptoms and signs. Moreover, we were convinced that he had end-stage heart failure at this point because he presented only one month after CRT-D implantation, indicating that he was a CRT non-responder.

His symptoms and urinary output improved after we began combined therapy with dobutamine, intravenous infusion of furosemide, and oral tolvaptan. However, after three days we could not continue appropriate doses of tolvaptan and furosemide because of the patient’s sleep disorder resulting from frequent nocturnal urination and the patient’s refusal allow the use of an indwelling urinary catheter. His urine volume decreased after the third day of hospitalization, and paroxysmal atrial fibrillation with rapid ventricular response developed after the tolvaptan was discontinued. Finally, a relapse of his acute decompensated heart failure occurred with an increased respiratory rate and a higher Modified Borg Scale score.

Because the patient refused mechanical ventilation, we discussed the case with our hospital’s multidisciplinary team for heart failure and with the patient and his family. Based on these discussions, and with the patient’s informed consent, on the sixth hospital day, we decided to introduce the intravenous infusion of oxycodone, 10 mg/day, as palliative treatment. We did not select morphine because of the potential side effects, such as respiratory depression, that could result from the accumulation of this medication due to his renal dysfunction. We also continued our efforts to maintain his cardiac output, volume, and oxygenation using other medications and non-invasive positive pressure ventilation.

Shortly after the initiation of oxycodone, the patient’s Modified Borg Scale score improved without a change in his respiratory rate. Simultaneously, we restarted the oral tolvaptan after the patient gave informed consent for the placement of an indwelling urinary catheter. Moreover, we performed electrical cardioversion for his paroxysmal atrial fibrillation on hospital day seven, and he regained a sinus rhythm.

The administration of oxycodone satisfactorily relieved

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**Table. Modified Borg Scale.**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Breathlessness</td>
</tr>
<tr>
<td>0.5</td>
<td>Very very slight (just noticeable)</td>
</tr>
<tr>
<td>1</td>
<td>Very slight</td>
</tr>
<tr>
<td>2</td>
<td>Slight Breathlessness</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Somewhat severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe breathlessness</td>
</tr>
<tr>
<td>6</td>
<td>Very severe breathlessness</td>
</tr>
<tr>
<td>7</td>
<td>Very severe (almost maximum)</td>
</tr>
<tr>
<td>8</td>
<td>Maximum</td>
</tr>
</tbody>
</table>

The modified Borg Scale score that documented the patient’s respiratory discomfort was recorded based on the current level of the patient’s subjective evaluation or the records of nurses involved in his treatment during stay in our coronary care unit.

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**Figure 1. A chest X-ray reveals cardiomegaly with mild pulmonary congestion and no pleural effusion.**
the patient’s dyspnea except for a temporary exacerbation with an increased Modified Borg Scale score due to an oxycodone dose reduction from 10 mg/day to 5 mg/day. We were also administering dobutamine and milrinone to maintain his cardiac output and tolvaptan to decrease his excessive systemic volume. On the other hand, the administration of oxycodone did not affect his respiratory rate and did not cause any excessive respiratory depression although it did mitigate his dyspnea as reflected by a decrease in his Modified Borg Scale score from 10 to 2 regardless of the oxygen flow rate and oxygen saturation.

We began reducing the oxycodone dose on the 26th day of hospitalization. By hospitalization day 29, his condition had become stable (New York Heart Association functional class 2), his cardiothoracic ratio had improved from 68% to 57%, his estimated glomerular filtration rate had improved from 22 to 60 mL/min, and we reduced his oxycodone to 5 mg/day. He left our intensive care unit on the 31st day of hospitalization with a small amount of dobutamine and without oxycodone.

We herein present the case of a patient with dyspnea secondary to decompensated end-stage heart failure and renal dysfunction whose dyspnea was successfully treated with oxycodone. We also managed his heart failure by increasing his cardiac output and reducing his volume overload. The patient’s Modified Borg Scale score continued to decline after the administration of oxycodone without any adverse opioid effect such as respiratory depression, and he was successfully discharged from the intensive care unit.

It is very difficult to elucidate precisely which therapies improved the patient’s symptoms and signs of heart failure because we performed various treatments simultaneously on admission. However, we believe that the oxycodone played a key role in the alleviation of his dyspnea and good clinical outcome based on changes in his Modified Borg Scale score and respiratory rate that were unrelated to the management of his heart failure. Moreover, we believe that management of his atrial fibrillation also played a key role in his clinical course and that the sympathetic inhibitory action of oxycodone facilitated the recovery and maintenance of a sinus rhythm after defibrillation, thereby favorably affecting the patient’s outcome.

Opioids are commonly used as a palliative treatment to alleviate various symptoms in the terminal stage of heart failure (7) when the clinical goal is no longer to prolong life. Using opioids to manage dyspnea is an important strategy for alleviating pain in patients with terminal-stage heart failure (1, 2, 6) regardless of the treatment goal (prolonging life versus palliation). Furthermore, this strategy can play a key role in preventing a worsening of heart failure in these terminally ill patients, because dyspnea can stimulate the sympathetic nervous system if untreated, which can exacerbate the condition leading to medically refractory heart failure.

On the other hand, it has been reported that in chronic heart failure patients neither oral morphine nor oral oxycodone...
Figure 4. Clinical course including medications, changes in the respiratory rate and the modified Borg Scale score, and various laboratory markers while in our coronary care unit.

done improved the dyspnea index compared to a placebo (8). Peacock et al., in their retrospective study, reported that morphine is associated with an increased incidence of adverse events in acute decompensated heart failure. They found a greater incidence of mechanical ventilation, prolonged hospitalization, intensive care unit admissions, and death (9). Currently, there is no consensus regarding the use of opioids in patients with heart failure. Therefore, further studies investigating the efficacy of opioids in patients with heart failure are needed.

Moreover, the different effects of morphine and oxycodone in patients with heart failure also require further study. Morphine is metabolized to morphine-3-glucuronide and morphine-6-glucuronide by the liver, and these are excreted by the kidney (10). Morphine-3-glucuronide has no pharmacological activity (11). Conversely, morphine-6-glucuronide is more pharmacologically active than morphine, and the formation of morphine-6-glucuronide is equivalent to approximately 10% of the morphine dose (10, 12, 13). Morphine is associated with a high probability of adverse effects, such as respiratory depression, in patients with renal insufficiency due to the accumulation of morphine-6-glucuronide (14). Therefore, it may be difficult to establish morphine as a reliable first-line agent in patients with end-stage heart failure because renal insufficiency is common in these patients (15).

Oxycodone is metabolized into noroxycodone and oxy-morphine by the liver, and these are then excreted by the
kidney. However, most oxycodone is metabolized into nortoxycodone which has no pharmacological activity, while only a small amount is metabolized to oxymorphone which is more pharmacologically active than oxycodone (16, 17). Oxycodone is less likely to cause side effects compared with morphine because the accumulation of the pharmacologically active metabolite oxymorphone is less than that of morphine-6-glucuronide in patients with renal insufficiency. Therefore, oxycodone may prove to be a reliable first-line agent in patients with end-stage heart failure and renal insufficiency. On the other hand, few investigators have evaluated the efficacy of oxycodone for the management of dyspnea (8, 18), and the safety of oxycodone for the management of dyspnea in patients with heart failure has thus not been established. Therefore, it is important that a multidisciplinary team for heart failure is involved in the decision to use oxycodone in this patient population. Further, the patient and the patient’s family should be fully informed about the expected results and uncertain safety of oxycodone treatment for dyspnea in patients with heart failure before consent is requested.

On the other hand, we must remember that palliative care does not always consist of opioid administration alone. A comprehensive approach including multidisciplinary management, dedicated nursing care, and the administration of analgesics besides opioids is commonly utilized. Furthermore, our approach to symptom alleviation should be comprehensive, based not only on the patient’s pathophysiology, but also on the patient’s social background and beliefs about death and input from the patient’s family members.

In conclusion, oxycodone may be a reliable first-line agent for the treatment of dyspnea in patients with end-stage heart failure and renal insufficiency. In our case, oxycodone successfully alleviated the symptoms without causing any respiratory depression, thereby suggesting its value for cases where prolonging life is the goal and for palliative care.

The authors state that they have no Conflict of Interest (COI).

References

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