Successful treatment with ivabradine in a β-blocker refractory patient with acute decompensated HFrEF

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Abstract

Ivabradine is an established treatment for chronic heart failure with reduced ejection fraction (HFrEF) but not for acute heart failure. β-blocker up-titration is often not possible because of its negative inotropic effect (NIE). Ivabradine has no NIE; therefore, it may be preferred over β-blockers in patients with acute decompensated HFrEF.

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Abstract

Ivabradine is an established treatment for chronic heart failure with reduced ejection fraction (HFrEF) but not for acute heart failure. β-blocker up-titration is often not possible because of its negative inotropic effect (NIE). Ivabradine has no NIE; therefore, it may be preferred over β-blockers in patients with acute decompensated HFrEF.

Key Clinical Message

Due to the negative inotropic effect (NIE) of β-blockers, their up-titration is often not possible in patients with acute decompensated HFrEF. Since ivabradine has no NIE, it may be preferred over β-blockers in such cases.

Introduction

Ivabradine is a selective I_f channel inhibitor that reduces only heart-rate and is an established treatment for chronic heart failure with reduced ejection fraction (HFrEF).[1-3] Ivabradine has been reported to reduce hospitalizations for heart failure and cardiovascular deaths similar to beta-blockers, but not for its effect on acute decompensated heart failure (ADHF).[4] Inappropriate tachycardia associated with HFrEF is a clinical symptom of ADHF, and appropriate initial treatment is important to improve prognosis.

Considering the available evidence in chronic heart failure, β-blockers are often used to treat ADHF with inappropriate tachycardia. However, patients often experience intolerance to β-blockers because of its negative inotropic effect (NIE), which demands alternative treatments without NIE for ADHF with inappropriate tachycardia in clinical practice. In this study, we have reported a case of β-blocker refractory patient with acute decompensated HFrEF with hypotension due to inappropriate sinus tachycardia successfully treated with ivabradine. Thus, we believe that ivabradine may play an important role in the acute heart failure treatment.

Case history/Examination

A man in his 50s who had been treated for cancer therapy-related cardiac dysfunction (CTRCD) with low left ventricular ejection fraction (LVEF) was admitted to our hospital because of ADHF. Fourteen years ago, he received chemotherapy consisting of rituximab (total 1500 mg/m^2), cyclophosphamide (total 5200 mg/m^2), doxorubicin (total 360 mg/m^2), vincristine, and prednisolone for malignant lymphoma. The next year, the patient underwent consolidation therapy, autologous transplantation, and radiotherapy (40 Gy in 27 fractions) and has been in remission since then.

On admission to the previous hospital, he had blood pressure of 90/66 mm Hg and heart rate of 120 bpm with regular rhythm. Subjective symptoms, such as palpitations and shortness of breath, were equivalent to New York Heart Association (NYHA) class IV. The patient had no infection and trauma before the admission.

The patient was administered a β-blocker carvedilol at a dose of 3.75 mg/day. Due to inappropriate tachycardia caused by hemodynamic instability, the carvedilol dose was increased. However, heart-rate reduction was not achieved because the NIE of the β-blocker exacerbated hypotension.

Differential diagnosis, investigations and treatment

On admission to our hospital, his blood pressure was 84/62 mm Hg; his heart-rate was 120 bpm. An electrocardiogram (ECG) revealed sinus tachycardia with a narrow QRS duration, and the heart-rate was >100 bpm (Figure 1). The chest x-ray film showed a cardiothoracic ratio of 42%, indicating the absence of pulmonary congestion or pleural effusion. Echocardiography showed a left ventricular end-diastolic diameter

of 55 mm and diffuse hypokinesis with an LVEF of 24%. The left atrial diameter was 40 mm, and the overlap of E and A waves in transmitral flow was revealed (Figure 2).

On admission, biochemical analysis showed blood urea nitrogen, creatinine, eGFR, and BNP levels of 55.3 mg/dL, 1.88 mg/dL, 30 mL/min/1.73 m^2, and 120 pg/mL, respectively. Thyroid-stimulating hormone, FT4 levels were within normal ranges. The serum creatine kinase level was 50 U/L (CK-MB < 4 ng/mL). The Holter ECG showed only sinus tachycardia and did not detect atrial fibrillation, non-sustained ventricular tachycardia and paroxysmal supraventricular tachycardia.

Involvement of thyroid function as a cause of sinus tachycardia was ruled out. Coronary angiography was performed in the previous hospital and showed no stenosis or obstruction, ruling out the possibility of heart failure due to ischemic heart disease. Based on the investigation, we confirmed that inappropriate sinus tachycardia caused ADHF in the patient with HFrEF. After admission to our hospital, inappropriate sinus tachycardia persisted, and his brain natriuretic peptide (BNP) level increased to 303 pg/mL.

Outcome and follow-up

Since the symptoms of heart failure persisted, and his heart-rate was over 70 bpm despite the treatment with the maximum tolerated dosage of carvedilol, the patient was administered 5 mg/day of ivabradine per os. After 10 days, his heart-rate decreased to <100 bpm, and his systolic blood pressure recovered to approximately 110 mm Hg. After we increased the ivabradine dosage to 10 mg/day, his heart-rate further decreased to 70 bpm without hypotension. His heart failure symptoms also improved and corresponded to NYHA Class III. Echocardiography showed that the LVEF improved to 36% without the overlap of E and A waves (Figure 3). After three months of ivabradine administration, his heart failure symptoms improved to NYHA Class II with a BNP level of 12 pg/mL, and echocardiography showed 56% improvement in the LVEF (Figure 4).

Discussion

ADHF with inappropriate tachycardia is a clinical symptom of HFrEF. With an elevated heart-rate, ventricular contractility increases in the normal myocardium, whereas it decreases in the failing myocardium.[5] Consequently, inappropriate tachycardia in heart failure induces hypotension and hemodynamic instability. In our case, the patient's heart-rate was >100 bpm and the echocardiography showed the overlap of E and A waves, which was suspicious for inappropriate sinus tachycardia.

β-blockers are not only a key agent in the management of chronic heart failure, but also the most common initial therapy for inappropriate sinus tachycardia.[3,6] However, they cause temporary symptomatic hypotension, low cardiac output states, and worsening heart failure due to their NIE.[7] β-blockers are associated with 41% relative increase in the risk of hypotension, and low systolic blood pressure (<120 mm Hg) is associated with a high risk of in-hospital and post-discharge mortality.[8,9] Because these risks are anticipated to increase further, especially during ADHF, the β-blocker up-titration was not possible for inappropriate sinus tachycardia that led to hemodynamic instability in the patient with HFrEF.

In contrast, ivabradine is the specific heart-rate lowering agent without NIE, while preserving ventricular contractility in chronic heart failure.[10] The absence of an NIE is an important consideration when selecting treatment for ADHF. Ivabradine may be a more appropriate treatment, especially for patients with HFrEF suffering from inappropriate sinus tachycardia leading to ADHF. The CONSTATHE-DHF study reported ivabradine as a potentially useful treatment for patients with ADHF because it reduces heart-rate while improving left and right ventricular functions.[11] Although the current indication for ivabradine is based on the results of the SHIFT trial, this study did not include patients who were discharged from the hospital for ADHF; therefore, the effects of ivabradine in these patients were unclear. However, the ETHIC-AHF trial suggested that early therapy with ivabradine is feasible and safe in patients with ADHF in HFrEF.[12] The SHIFT-AHF trial, which involves ivabradine administration in patients with ADHF, is ongoing. The results of this trial are expected, and our case suggests that ivabradine may be preferable for patients with ADHF and HFrEF.

Another reason for selecting ivabradine for ADHF is its potential to intervene earlier than β-blockers in long-term prognosis. β-blockers are associated with survival benefits in stable chronic heart failure. While the use of β-blockers significantly improves LVEF, reverses left ventricular maladaptive remodeling, and reduces all-cause mortality from months to years,[13] only a small percentage of patients with chronic heart failure can achieve the optimal dose of β-blockers due to their NIE. For example, in the SHIFT trial, only 25% patients were on optimal β-blocker doses.[3] In addition, although heart-rate reduction is associated with the use of β-blockers, no correlation with the dose of these agents has been found. In fact, the percentage of patients who achieved an optimal heart-rate with β-blocker administration is small.[14] For heart-rate reduction, higher than the optimal doses of β-blockers are mostly required, but hemodynamic instability in patients with ADHF prevents their administration and up-titration. However, earlier administration of β-blockers is desirable to improve long-term prognosis. Ivabradine also has the effect of reducing hospitalizations for heart failure and cardiovascular deaths. In the previous report, ivabradine showed not only a prognostic benefit for heart-rate control, but also a prognostic significance for the time required to achieve this control.[15] In patients with ADHF, even if hemodynamic instability is present, administration of agents as soon as possible after admission is essential to improve the prognosis of heart failure. Therefore, ivabradine may be preferred over β-blockers in these patients.

In our patient, CTRCD was the underlying cause of heart failure. A common manifestation of radiation-induced heart disease is pericarditis.[16] Pericarditis causes diastolic dysfunction. In patients with diastolic dysfunction, due to constrictive pericarditis, appropriate heart-rate is associated with less heart-failure recurrences.[17] Our patient had diastolic dysfunction combined with inappropriate sinus tachycardia, leading to ADHF. However, it is unclear whether ivabradine has a beneficial effect in all such patients.

Conclusion

β-blockers are commonly used to treat ADHF with inappropriate tachycardia. Due to its NIE, its up-titration is not possible in the case of inappropriate sinus tachycardia, which leads to hemodynamic instability in a patient with HFrEF. Therefore, administration of ivabradine may be preferable to β-blockers in patients with ADHF, who have inappropriate sinus tachycardia with HFrEF, as it improves long-term prognosis without NIE.

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Author contributions

TI: involved in analysis and interpretation of the patient's data; conception, design, and drafting of the manuscript. KM: involved in conception, design, critical feedback, and revision of the manuscript. WK: involved in analysis and interpretation of the patient's data and revision of the manuscript.

TM: involved in revision and final approval of the manuscript. All authors discussed the case and commented on the manuscript at all stages.

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