Case Report

Two cases of wide QRS complex tachycardia caused by anamorelin

Yutaro Okidono (MD) *, Jun Osada (MD), Kazuya Otsu (MD), Shinya Kowase (MD), Hajime Aoki (MD), Kazuhiko Yumoto (MD, PhD)

Department of Cardiovascular Medicine, Yokohama Rosai Hospital, Kanagawa, Japan

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A B S T R A C T

Anamorelin is prescribed for cancer cachexia treatment. Anamorelin is a ghrelin receptor antagonist and exerts a sodium channel blockade effect, possibly inducing disorders of the cardiac conduction system. We herein report two cases of wide QRS complex tachycardia caused by anamorelin. In both cases, the patients had liver dysfunction. Anamorelin is mainly metabolized in the liver; hence, sodium channel blockade by anamorelin during liver dysfunction can cause serious side effects, including wide QRS complex tachycardia, similar to flecainide toxicity.

The differential diagnosis of wide QRS tachycardia caused by anamorelin can be challenging because conventional electrocardiogram criteria cannot be applicable in patients with drug intoxication. It can worsen the situation for the use of antiarrhythmic drugs for wide QRS tachycardia. The appropriate treatment is supportive care until anamorelin is metabolized. To our best knowledge, this is the first study to report the life-threatening adverse effects of anamorelin.

Learning objective: Anamorelin is prescribed for cancer cachexia treatment. Anamorelin can cause wide QRS complex tachycardia. Our findings in the two cases we encountered indicate that we should be aware of wide QRS complex tachycardia in patients taking anamorelin, especially if they have liver dysfunction. We should suspect the condition to be the adverse effect of anamorelin and monitor the electrocardiogram and blood test findings regularly to prevent this fatal side effect.

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Introduction

Anamorelin is the drug of choice for cancer cachexia and is effective in improving weight loss and anorexia [1,2]. It first became available in Japan in April 2021. Anamorelin is a selective ghrelin receptor antagonist. Ghrelin is an endogenous ligand of the growth hormone secretagogue receptor, which is distributed in many tissues such as the pituitary gland, hypothalamus, stomach, and myocardium [3]. By targeting the pituitary gland, it aids in the release of growth hormone, and by targeting the hypothalamus, it increases appetite [4]. Consequently, they lead to weight gain in patients with cancer cachexia. There is a strong association between body mass index and mortality [5]; hence, anamorelin can improve prognosis. However, anamorelin also exerts a sodium channel blockade effect, causing serious side effects, including sinus arrest, atrio-ventricular block, and dysrhythmias, more likely in patients with liver dysfunction. Thus far, there has been no report of wide QRS complex tachycardia caused by anamorelin. In this study, we report two cases of tachycardia due to wide QRS complex tachycardia caused by anamorelin, one in a 56-year-old woman and the other in a 67-year-old woman.

Case reports

The first patient was a 56-year-old woman. She had stage IV appendix cancer and received chemotherapy. She had no history of heart disease. She was admitted to the hospital for bile duct stenosis and cholangitis associated with lymph node metastasis. On admission, an electrocardiogram (ECG) showed sinus rhythm: heart rate (HR), 83 beats/min; PR interval, 138 ms; QRS duration, 88 ms; and QTc interval, 413 ms. Laboratory data on initiation of anamorelin administration, half a month before admission, showed prothrombin time (PT), 94%; albumin (Alb) level, 3.0 g/dL; and total bilirubin (T-Bil) level, 0.99 g/dL; she had no encephalopathy and ascitic fluid; therefore, she had a Child-Pugh class A score of 6. The patient had an appetite, so she had not taken anamorelin before admission. She started to take 100 mg of...
anamorelin since admission. On the fifth day of hospitalization, she complained of dyspnea during rehabilitation; her vital signs were as follows: blood pressure, 106/93 mm Hg; body temperature, 36.5 °C; HR, 145 beats/min; and respiratory rate, 24 breaths/min. The consciousness level was preserved. ECG demonstrated a remarkable wide QRS complex tachycardia: HR, 145 beats/min; and QRS duration, 420 ms. The P wave could not be identified (Fig. 1A). Lidocaine (100 mg) and amiodarone (150 mg) were administered intravenously, and synchronized cardioversion at 100 J and 150 J was delivered. Her HR was lowered temporarily, but the effect was limited and tachycardia recurred immediately. We found a remarkable intraventricular conduction delay (Fig. 2). It was presumed that myocardial infarction or electrolyte abnormalities were the cause of wide QRS tachycardia. However, she did not have chest pain. Transthoracic echocardiography showed no asynergy. In addition, laboratory data showed serum sodium, 132 mEq/L; potassium, 4.5 mEq/L; and magnesium, 2.1 mg/dL, and the results indicated no electrolyte abnormalities. Laboratory data also showed PT, 33%; Alb level, 2.1 g/dL; and T-Bil level, 1.43 g/dL, and she had no encephalopathy and ascitic fluid. Hence, she had a Child–Pugh class B score of 9. We confirmed the side effect of medicines and suspected anamorelin; hence, we stopped prescribing anamorelin. After that, wide QRS complex tachycardia was observed intermittently, and it disappeared after several hours. Her ECG findings became normal on the next day (Fig. 1B). The patient died on the 24th day of hospitalization due to exacerbation of the underlying disease.

The second patient was a 67-year-old woman. She had stage IVc appendix cancer with multiple lung and liver metastases and received chemotherapy. She had no history of cardiac disease. She was prescribed 100 mg of anamorelin for cancer cachexia. On initiation of anamorelin administration, ECG showed HR, 88 beats/min; PR interval,
186 ms; QRS duration, 58 ms; and QTc interval, 400 ms. Laboratory data demonstrated PT, 103%; Alb level, 3.5 g/dL; and T-Bil level, 0.55 g/dL, and she had no encephalopathy and a mild ascitic fluid. Hence, her Child–Pugh class A score was 6. One and a half months later, she felt weak and had difficulty walking. On arrival to the emergency department, her vital signs were as follows: blood pressure, 75/55 mm Hg; body temperature, 37.1 °C; HR, 120 beats/min; and respiratory rate, 26 breaths/min. The consciousness level was preserved. The ECG findings demonstrated a remarkably wide QRS complex tachycardia: HR, 101 beats/min; and QRS duration, 445 ms. The P wave could not be identified (Fig. 3A). Her Child–Pugh class B score was 8. Amiodarone (150 mg) was then administered intravenously, and the tachycardia stopped. However, the effect was limited, and she had disorders of the cardiac conduction system. She had no chest pain, and myocardial infarction and myocarditis were negative by transthoracic echocardiography. In addition, laboratory data showed serum natrium, 125 mEq/L; potassium, 5.2 mEq/L; and magnesium, 2.2 mg/dL. There were no electrolyte abnormalities to induce arrhythmia. Laboratory data also showed PT, 64%; Alb level, 2.5 g/dL; and T-Bil level, 0.88 g/dL, and she had no encephalopathy and a mild ascitic fluid; hence, her Child–Pugh class B score was 9. At the time of admission, the patient had difficulty with food intake and oral medications, including anamorelin, which had been discontinued. On the fourth day of admission, her ECG findings became normal (Fig. 3B). The patient died on the 11th day of hospitalization due to exacerbation of the underlying disease.

**Discussion**

We encountered two cases of wide QRS complex tachycardia due to anamorelin. Approximately 10.7% of patients on anamorelin have cardiac conduction disorders [1]. Anamorelin is metabolized by CYP3A4, which is mainly present in the liver. Therefore, liver dysfunction delays the metabolism of anamorelin. Hence, anamorelin is contraindicated in patients with more than moderate liver dysfunction. In both cases, when anamorelin was initiated, there was mild liver dysfunction. However, liver function was poor due to cholangitis and liver metastases. Liver dysfunction may occur with cancer progression. Since anamorelin has a high protein binding rate, malnutrition tends to induce high blood levels of anamorelin. Patients with cancer have a high risk of liver dysfunction and malnutrition, and they induce increased blood levels of anamorelin. As a result, the discontinuation and reduction of anamorelin should be considered. Therefore, liver function tests and Child–Pugh scores should be regularly monitored. Initially, we suspected that our cases had myocardial infarction or electrolyte abnormalities; however, transthoracic echocardiography showed no obvious anomaly, and there were no serum electrolyte abnormalities. Hence, we suspected it to be an adverse effect of anamorelin. The patients had no medication which could disrupt the cardiac conduction system, except for anamorelin. Anamorelin has a sodium channel blockade effect and causes tachycardias similar to those at the time of flecainide intoxication. ECG is the most important tool for diagnosing cardiac conduction disorders due to anamorelin. ECG can demonstrate prolongation of the PR interval and remarkable widening of the QRS duration, which are also found in flecainide poisoning [6]. The QRS complex was too wide during tachycardia. Thus, we could not identify the P wave. The tachycardias did not meet ventricular tachycardia criteria, such as the Brugada criteria [7]. It was difficult to differentiate between ventricular and supraventricular tachycardia. It is presumed that the sodium channel block effect of anamorelin caused conduction delay and remarkable wide QRS complex tachycardia. Treatment for anamorelin-related cardiac toxicity aims at excreting anamorelin from the body. However, anamorelin is metabolized by the liver, and it also has a high protein binding rate and a large volume of distribution; hence, hydration and hemodialysis are ineffective. If a patient takes 100 mg of anamorelin, the half-life is approximately 9 h. While anamorelin is metabolized, cardiovascular support should be considered to avoid lethal arrhythmia. Cardioversion, overdrive pacing, and extracorporeal support should be provided for unstable rhythms, such as torsades de pointes. Ventricular dysrhythmias of flecainide poisoning can be treated with sodium bicarbonate to minimize the aggravation of the condition [6]. It may also be effective for treating wide QRS complex tachycardia due to anamorelin. Antiarrhythmic drugs are usually ineffective for treating this condition. These drugs should be avoided because they can worsen the sodium channel blockade effects due to anamorelin. We administered lidocaine and amiodarone because we suspected ventricular tachycardia. However, both antiarrhythmic drugs have sodium channel blockade effects, and they may have been involved in the recurrence of tachycardia due to the further prolongation of conduction disorders. For example, amiodarone inhibits the action of CYP3A4, a metabolic enzyme of anamorelin.

To conclude, wide QRS complex tachycardia is caused by anamorelin and is triggered by liver dysfunction. The adverse effect of anamorelin should be suspected when the cause of wide QRS complex tachycardia is unknown. ECG and blood test findings should also be regularly monitored to prevent this lethal side effect.

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Declaration of competing interest
The authors declare no conflict of interest.

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Fig. 3. (A) Electrocardiogram (ECG) taken in the emergency department. Heart rate (HR), 101 beats/min; and QRS duration, 445 ms. The P wave could not be identified.
(B) ECG taken on the 4th day in the hospital. HR, 108 beats per minute; sinus tachycardia; PR interval, 154 ms; QRS duration, 84 ms; and QTc interval, 367 ms.
References


