Amiodarone-Induced Hyponatremia Masked by Tolvaptan in a Patient with an Implantable Left Ventricular Assist Device

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Summary
A 43-year-old man was referred to our hospital in June 2014 because of severe heart failure. He was diagnosed with familial dilated cardiomyopathy and was administered oral tolvaptan and amiodarone for atrial and ventricular tachycardia. Since up-titration of carvedilol had failed and he was dependent on dobutamine, a left ventricular assist device (LVAD) was implanted. Tolvaptan and furosemide were both discontinued after LVAD implantation and he was discharged from the hospital. Thirteen months later, he was hospitalized for lethargy and hyponatremia of 108 mEq/L, with an antidiuretic hormone level of 2.5 pg/mL, which suggested syndrome of inappropriate antidiuretic hormone secretion (SIADH). We discontinued amiodarone and administered fludrocortisones. However, hyponatremia persisted for a few more days, eventually resulting in delirium and damage to the LVAD driveline. He received an urgent pump exchange and hyponatremia was gradually improved. We considered the possibility that amiodarone-induced SIADH was masked by tolvaptan therapy before LVAD implantation.

Key words: Dilated cardiomyopathy (DCM), Heart failure, Syndrome of inappropriate antidiuretic hormone secretion (SIADH), Delirium, Adverse effect

Hyponatremia is an electrolyte disorder commonly encountered in clinical practice, and dilutional hyponatremia is the most common form of the disorder. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is also a frequent underlying disorder in hospitalized patients. Hyponatremia is often complicated by advanced heart failure (HF), along with the increased excretion of sodium by diuretics. Tolvaptan, a vasopressin type 2 receptor antagonist, improves volume overload and hyponatremia in HF patients with insufficient response to loop diuretics and also may improve HF readmission rates in both HF patients with reduced ejection fraction (EF) and those with preserved EF. However, tolvaptan may mask the hyponatremia caused by SIADH in the context of a serious underlying disorder, and therefore may delay the appropriate management of the disorder or adverse effect once tolvaptan is discontinued. We here report an instructive case of amiodarone-induced SIADH masked by tolvaptan, in which delirium induced a severe driveline injury and necessitated the urgent pump exchange of a left ventricular assist device (LVAD).

Case Report
The patient was a 43-year-old man admitted to a previous hospital for de novo HF in June 2014. His mother and brothers had dilated cardiomyopathy (DCM) and his older brother died suddenly. Echocardiography showed reduced systolic function with an EF of 17% and he was subsequently referred to our hospital. On admission, physical examination showed a height of 173.4 cm, body weight of 58.2 kg, blood pressure of 96/60 mmHg, heart rate of 132 beats per minute, body temperature of 36.8°C, and oxygen saturation (SpO2) of 96% in room air. Cardiac auscultation revealed third and fourth heart sounds with a gallop rhythm.

Laboratory tests showed a hemoglobin level of 14.8 g/dL, serum sodium concentration of 139 mEq/L, serum potassium level of 4.4 mEq/L, serum chloride level of 107 mEq/L, creatinine level of 1.03 mg/dL, and total bilirubin level of 0.8 mg/dL. The B-type natriuretic peptide (BNP) level was markedly elevated to 2113.1 pg/mL. Electrocardiography revealed atrial tachycardia of 130 beats per minute with left ventricular high voltage. Echocardiography revealed dilatation of the left ventricle (LV) with diffuse hypokinesis; the diastolic dimension (Dd) was 72 mm and the systolic dimension (Ds) was 63 mm.
Clinical course: We provided a continuous infusion of dobutamine and milrinone, and administered oral enalapril 2.5 mg and carvedilol 1.25 mg. When we up-titrated carvedilol from 1.25 mg to 2.5 mg, his blood pressure decreased and he suffered from faintness. We reduced the carvedilol dose from 2.5 mg to 1.25 mg and administered an intravenous amiodarone infusion in an attempt to convert the atrial tachycardia to sinus rhythm. After successful conversion to sinus rhythm, we chose oral administration of amiodarone in place of intravenous infusion. Cardiac catheterization and endomyocardial biopsy were performed, and he was diagnosed with DCM. He could not be weaned from catecholamine infusion and was listed for heart transplantation. After 9 months in the hospital, he underwent implantable LVAD (HeartMate-II\textsuperscript{15}) surgery. After the implantation, tolvaptan and furosemide were discontinued, and carvedilol was up-titrated to 30 mg per day. The administration of amiodarone 100 mg per day was continued because non-sustained ventricular tachycardia was detected on an electrocardiogram.

One and a half months later, cardiomegaly on chest radiography improved and echocardiography showed an LVDd of 59 mm and EF of 38%. Cardiac catheterization and endomyocardial biopsy were performed, and he was diagnosed with DCM. He could not be weaned from catecholamine infusion and was listed for heart transplantation. After 9 months in the hospital, he underwent implantable LVAD (HeartMate-II\textsuperscript{15}) surgery. After the implantation, tolvaptan and furosemide were discontinued, and carvedilol was up-titrated to 30 mg per day. The administration of amiodarone 100 mg per day was continued because non-sustained ventricular tachycardia was detected on an electrocardiogram.

Six months after LVAD implantation, his echocardiography showed a significant reverse remodeling of the LV, with a Dd of 55 mm and EF of 42%. However, his blood chemistry still showed hyponatremia. Ten months after implantation, his serum sodium level again decreased to 123 mEq/L, and his hyponatremia was now considered to be drug-induced SIADH. Therefore, we reduced the dose of amiodarone from 100 mg to 50 mg per day. Still, 13 months after implantation, he was admitted to our hospital for malaise and lethargy. His serum sodium level, serum osmolality, BNP level, and ADH level were 108 mEq/L, 220 mOsm/kg, 21.3 pg/mL, and 2.5 pg/mL, respectively (Table). His plasma renin activity, plasma aldosterone concentration, adrenocorticotropic hormone (ACTH), and cortisol were 4.1 ng/mL/hour, 639 pg/mL, 37.2 ph/mL, and 19.6 μg/dL. He had no thyroid dysfunction (thyroid stimulating hormone 2.364 μU/mL, free-thyroxine 1.4 ng/dL) and we diagnosed his hyponatremia as a SIADH due to amiodarone. We discontinued amiodarone and started fludrocortisone. Four days later, because his serum sodium level improved to 113 mEq/L and his symptoms disappeared, he was discharged from the hospital. Then, 2 days later, he lapsed into a delirious
state which resulted in a severe injury of the LVAD driveline. He was urgently re-hospitalized for LVAD pump stoppage. Thanks to recovery of his native heart function with an LVEF of 48%, he had no organ damage during pump failure. On the second day of admission, an urgent pump exchange was undertaken. One month later, his serum sodium level had improved to 126 mEq/L, and the ADH level decreased to 0.6 pg/mL. He was safely discharged with a serum sodium level of 131 mEq/L.

**Discussion**

Amiodarone, a benzofuran derivative, is the most common antiarrhythmic drug in HF management. It was first developed in 1961 as an antianginal drug and since then, has been used extensively as a broad-spectrum antiarrhythmic agent. In addition to its superior effectiveness over other antiarrhythmic drugs, it is also useful for antiarrhythmic therapy in patients with advanced HF due to its low negative inotropic action. Despite these advantages, the use of amiodarone is associated with a relatively high incidence of adverse effects, making it a complicated drug to use safely. Amiodarone-induced hyponatremia is a rare complication that was first reported in 1996. Dutta, *et al* investigated previous 12 cases of amiodarone-induced SIADH in 2014. To the best of our knowledge, 16 cases of amiodarone-induced SIADH have been published thus far.

Hyponatremia is an electrolyte disorder frequently seen in severe HF, especially in the context of diuretic use. Tolvaptan, a vasopressin 2 receptor antagonist, is an aquaretic agent, and its effectiveness for severe HF even in LVAD patients has been reported. Heart failure patients with low cardiac output often also have hyponatremia with high levels of plasma ADH. In such patients, however, cardiac replacement therapy including LVAD implantation usually reverses serum sodium levels in accordance with dramatic decreases in plasma ADH levels. The marked changes in ADH levels are attributable to the correction of low cardiac output. Therefore, in this case, hyponatremia with high ADH levels was most likely not due to HF after LVAD implantation because we could not find any evidence of decreased output after surgery.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a biochemical manifestation of a wide variety of diseases, and the pathophysiology of SIADH is often multifactorial. However, there are a few case reports of SIADH induced by amiodarone, and the period between its administration to the appearance of SIADH varied from 3 days to 6 months. In our case, hyponatremia appeared 8 months following amiodarone initiation, and 2 weeks after LVAD implantation. SIADH due to amiodarone may be masked by the use of tolvaptan, and amiodarone had already caused SIADH before LVAD implantation. The elimination half-life after cessation of amiodarone therapy is said to be about 53 days for amiodarone and 61 days for desethylamiodarone, though the half-life appears to be longer in patients than in healthy subjects; therefore, a more extended time period is required to improve hyponatremia even after the discontinuation of amiodarone. SIADH should be recognized as a possible adverse effect of amiodarone, and if suspected, amiodarone should be discontinued as soon as possible to prevent persistent hyponatremia. The mechanism of SIADH-induced hyponatremia secondary to amiodarone is unknown. Many drugs can induce SIADH, possibly due to sensitization of the kidneys or stimulation of the release of ADH. Shavit, *et al* speculated that amiodarone might induce SIADH via its channel-modulating properties in renal or neural tissues. In our case, because the ADH levels were remarkably elevated even in the context of severe hyponatremia and were reduced after cessation of amiodarone, amiodarone-induced SIADH might be due to modulation of the channels related to the excretion mechanism of ADH in the pituitary gland.

A limitation of the present case report is that rechallenge of amiodarone might confirm the diagnosis of amiodarone-induced SIADH; however, rechallenge might also raise safety concerns in severe cases like this.

We here report a case of hyponatremia induced by SIADH due to amiodarone and consequent delirium that induced severe driveline injury and necessitated an urgent LVAD pump exchange. When amiodarone and tolvaptan are used in combination, it is necessary to keep in mind that marked hyponatremia may appear after the discontinuation of tolvaptan, since it may have been masking amiodarone-induced SIADH.

**Disclosures**

**Conflicts of interest:** None.

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