Pediatr Cardiol (2013) 34:1261–1263
DOI 10.1007/s00246-012-0373-x

CASE REPORT

Syndrome of Inappropriate Secretion of Antidiuretic Hormone Associated With Angiotensin-Converting Enzyme Inhibitor Administration

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Received: 15 December 2011 / Accepted: 8 May 2012 / Published online: 24 May 2012

Abstract Angiotensin-converting enzyme inhibitors (ACEI's) are an important medication in the treatment of congestive heart failure. However, ACEIs may cause harmful side effects, such as the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), which is a rare but important side effect. We describe here a case of SIADH associated with ACEI administration in a 6-year-old boy with restrictive cardiomyopathy. After recovery from acute exacerbation of congestive heart failure by tolvaptan administration, an ACEI (cilazapril) was started to decrease the production of angiotensin II, which upregulates serum antidiuretic hormone secretion. The patient's heart failure symptoms worsened, including accumulation of right pleural effusion and ascites, after the initiation of ACEI administration. Cessation of ACEI administration dramatically improved his symptoms. Because it is difficult to distinguish SIADH associated with ACEI from worsening congestive heart failure, the possibility of fluid retention due to ACEI administration should always be considered when this agent is administered to patients with heart failure.

Keywords Angiotensin II · Angiotensin-converting enzyme inhibitor · Congestive heart failure · Syndrome of inappropriate secretion of antidiuretic hormone

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Introduction

Angiotensin-converting enzyme inhibitors (ACEI's) are an important medication for the medical treatment of congestive heart failure. Administration of an ACEI can cause some harmful reactions, including the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), which is one of the most important side effects of this agent. There are few reported cases of this adverse effect [2, 4]. It is essential to be aware of this possible complication because the symptoms of SIADH resemble those seen in patients with worsening congestive heart failure. Here, we describe a case of SIADH associated with ACEI administration in a boy with cardiomyopathy.

Case Report

A 6-year-old boy with restrictive cardiomyopathy was admitted to our medical center and was awaiting cardiac transplantation. Although his heart failure symptoms had deteriorated secondary to enteritis, he recovered after tolvaptan administration. Tolvaptan is a vasopressin V2 receptor antagonist that causes increased urine output. Before the start of tolvaptan administration, his serum antidiuretic hormone (ADH) level was increased (14.10 pg/ml) despite hyponatremia (121 mEq/l). Because increased ADH secretion could make heart failure worse, administration of an ACEI (cilazapril) was initiated to inhibit the production of angiotensin II, which upregulates ADH secretion [1], after the patient had recovered from the worsening of the heart failure associated with his enteritis.

After the start of ACEI administration, the patient's urinary volume mildly decreased, and his body weight gradually increased. Furthermore, he developed pleural

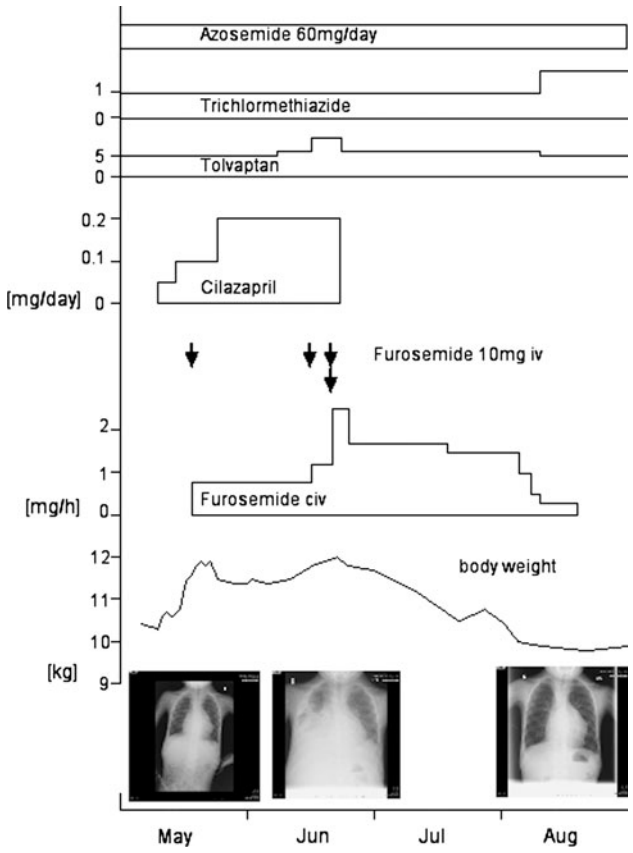

Fig. 1 Clinical course. *CIV* continuous intravenous infusion; *IV* intravenous

effusion and ascites collection (Fig. 1). His serum creatinine level was not increased, and his total creatinine excretion was maintained. Furosemide administration did not improve the worsening of his symptoms. His hyponatremia was exacerbated, and therefore the tolvaptan was uptitrated (from 5 to 9 mg for 10 kg boy). This was partially effective: His serum sodium concentration increased from 112 to 121 mEq/l; his plasma osmolarity increased from 262 to 265 mOsm/kg H_2O; and his urine osmolarity decreased from 246 to 222 mOsm/kg H_2O. However, his symptoms were gradually worsening. At this point, the ACEI was stopped based on the suspicion of SIADH associated with ACEI. After cessation of the ACEI, the patient's urine volume increased, and the fluid collection gradually disappeared. His serum sodium concentration and plasma osmolarity both increased (121–132 mEq/l and 265–270 mOsm/kg H_2O, respectively), and his urine osmolarity (from 222 to 201 mOsm/kg H_2O) decreased.

Discussion

SIADH associated with ACEI has been reported as a complication resulting from the use of enalapril [2] and lisinopril [4] in adult patients. Although the role of ACEIs in SIADH is not clear, the possible mechanism is believed to be that ACEIs block the conversion of angiotensin I to angiotensin II, consequently increasing the concentration of angiotensin I. After low to moderate doses of an ACEI, ACE blocking may be complete in peripheral organs, but there may also be enough unblocked enzyme in the brain to allow the increased amounts of blood-borne angiotensin I reaching it to be converted to angiotensin II, even though ACEIs can cross the blood–brain barrier [1]. Thus, the increased angiotensin II enhances ADH secretion in the brain.

It is difficult to diagnose SIADH secondary to the use of an ACEI when ACEIs are being used for the treatment for congestive heart failure because many of the features are identical. In SIADH, basically, intracellular fluid volume increases, and edema does not occur. However, our patient had pleural effusion and ascites collection. He also had hyponatremia with increased extracellular fluid before the start of ACEI administration, which indicated increased ADH secretion (ADH 5.24 pg/ml and Na 121 mEq/l). In this way, the symptoms of SIADH in heart failure patients resemble the symptoms of deteriorating heart failure. The diagnosis of SIADH associated with ACEI administration is not easy in this condition because many of the features of worsening congestive heart failure and SIADH are identical.

In the case presented here, tolvaptan administration did not fully improve the condition of SIADH associated with ACEI despite adequate dosing of tolvaptan based on the dosage set for adults set in Japan (15 mg daily). However, the dosage of tolvaptan administration for an adult patient may be as high as 30 or 60 mg daily as reported in the literature [3]. An alternative in the management of this case may have been a further increase of the tolvaptan as necessary.

Conclusion

When administering ACEIs for heart failure patients, SIADH should be considered as a rare but possible complication associated with the use of this agent.

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