Combination Therapy of Angiotensin II Receptor Blocker and Thiazide Produces Severe Hyponatremia in Elderly Hypertensive Subjects

Hodaka Yamada, Tomoko Asano, Atsushi Aoki, Aki Ikoma, Masashi Yoshida, Ikuyo Kusaka, Masanobu Kawakami, Masafumi Kakei and San-e Ishikawa

Abstract

Thiazide diuretics are known to produce severe hyponatremia as well as hypokalemia. The present study demonstrated severe hyponatremia in three hypertensive patients who had received combination therapy consisting of an angiotensin II receptor blocker (ARB) and thiazide. The serum sodium (Na) levels in all three cases were markedly reduced to below 116 mmol/L, and the patients exhibited augmented urinary excretion of Na with a reduced circulatory blood volume. After withdrawing the ARB and thiazide treatment, the serum Na levels normalized within one to two weeks. Combination therapy with ARBs and thiazide may cause hyponatremia in elderly patients.

Key words: hyponatremia, elderly subjects, thiazide diuretics, arginine vasopressin

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Introduction

Hyponatremia is a common electrolyte disorder in elderly subjects. It is important to evaluate the pathophysiology of hyponatremia and provide appropriate treatment. Recently, combination therapy consisting of angiotensin II receptor blockers (ARBs) and thiazide diuretics has become commonly used to treat hypertension in elderly patients. Previous clinical trials have shown that thiazide diuretics are effective in preventing cardiovascular events in elderly subjects (1-3). However, little attention has been paid to the occurrence of thiazide diuretic-induced hyponatremia. We encountered three elderly patients who were referred to our hospital due to severe hyponatremia. All three patients had been treated with ARBs and thiazide diuretics. The purpose of this case report is to describe the characteristics of these three hyponatremic elderly patients and discuss the pathophysiology of thiazide-induced hyponatremia.

Case Reports

Case 1

An 85-year-old man had received combination treatment consisting of 80 mg of valsartan potassium and 12.5 mg of hydrochlorothiazide for hypertension for the past year. His serum sodium (Na) level had decreased to 134 mmol/L at the latest outpatient clinic visit in October 2010; however, he displayed no symptoms and had no history of chronic vomiting or diarrhea. He was referred to Jichi Medical University Saitama Medical Center in October 2010 for a further examination. The physical findings upon hospitalization showed a height of 150 cm and a body weight of 55 kg, with a body mass index of 24.4 (Table 1). The patient’s blood pressure was 187/100 mmHg, and his pulse rate was 90 beats/min with a regular rhythm. His skin turgor was reduced. There were no abnormal heart sounds or signs of liver enlargement or leg edema, and the neurological findings were normal. The laboratory findings showed a serum Na level of 116 mmol/L, a potassium (K) level of 3.1...
mmol/L and a chloride (Cl) level of 80 mmol/L (Table 2). However, the levels of urinary excretion of Na, K and Cl were all elevated. The plasma renin activity was 1.2 ng/mL/h, while the plasma aldosterone concentration was 41 pg/mL and the serum cortisol level was 12.9 μg/dL. The urinary osmolality was 375 mOsm/kg and the plasma arginine vasopressin (AVP) level was 1.7 pg/mL, despite a plasma osmolality of 226 mOsm/kg. The patient was physically dehydrated and had an exaggerated urinary excretion of Na with a relatively high level of plasma AVP. The plasma brain natriuretic peptide level was normal. We suspected that the combination therapy with valsartan and hydrochlorothiazide produced the hyponatremia. The patient received no other drugs that cause hyponatremia. The antihypertensive drug was withdrawn, and the patient consumed only 10 g/day of dietary sodium. Approximately one week later, the serum Na level increased to 134 mmol/L and the urinary excretion of Na and K decreased.

Table 2. Laboratory Data in the Three Cases

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td>187/100</td>
<td>148/76</td>
<td>141/60</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>116</td>
<td>106</td>
<td>116</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.1</td>
<td>4.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>80</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>16</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.34</td>
<td>0.5</td>
<td>0.64</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>3.7</td>
<td>3.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>112</td>
<td>139</td>
<td>68</td>
</tr>
<tr>
<td>Urine Na (mmol/L)</td>
<td>72</td>
<td>63</td>
<td>96</td>
</tr>
<tr>
<td>Urine K (mmol/L)</td>
<td>22.8</td>
<td>51.2</td>
<td>27.2</td>
</tr>
<tr>
<td>Uosm (mOsm/kg)</td>
<td>375</td>
<td>ND</td>
<td>585</td>
</tr>
<tr>
<td>PAC (pg/mL)</td>
<td>41.0</td>
<td>35.1</td>
<td>24.1</td>
</tr>
<tr>
<td>PRA (ng/mL/h)</td>
<td>1.2</td>
<td>5.0</td>
<td>1.9</td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>22.9</td>
<td>21.1</td>
<td>88.7</td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>12.9</td>
<td>17.4</td>
<td>18.6</td>
</tr>
<tr>
<td>AVP (pg/mL)</td>
<td>1.7</td>
<td>1.1</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Case 2

An 86-year-old man was diagnosed with hypertension. He had received combination therapy consisting of 25 mg of telmisartan and 12.5 mg of hydrochlorothiazide for the past year. One week prior to visiting the Jichi Medical University Saitama Medical Center in November 2011, he felt lethargic and nauseous. He exhibited clear consciousness, although severe hyponatremia (106 mmol/L) was observed. He was admitted to our hospital for a further examination. He had no history of chronic vomiting or diarrhea. His height was 160 cm and his body weight was 50 kg (Table 1). His blood pressure was 148/76 mmHg and his pulse rate was 107 beats/min with a regular rhythm. There were no abnormal findings in the head, neck, chest or abdomen; however, the skin turgor was reduced. The laboratory findings showed a serum Na level of 106 mmol/L, a K level of 4.1 mmol/L and a Cl level of 76 mmol/L (Table 2). The levels of urinary excretion of Na, K and Cl were 63, 51.2 and 69 mmol/L, respectively. The patient’s renal function was normal. The serum cortisol level was 17.4 μg/dL, while the plasma renin activity was as high as 5.0 ng/mL/h and the plasma aldosterone concentration was 35.1 pg/mL. Brain computed tomography was unremarkable. We suspected a diagnosis of drug-induced hyponatremia and thus discontinued the combination treatment. No other drugs that cause hyponatremia were given. The infusion of 3% NaCl was temporarily administered to treat the hyponatremia, increasing the serum Na level to 124 mmol/L. Thereafter, the patient consumed 10 g/day of dietary sodium, and the serum Na level normalized within 15 days.

Case 3

A 79-year-old man had hypertension. He had tried to restrict his salt intake for the past year. He visited a local clinic where he received combination therapy consisting of 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide one month prior to admission to our hospital. Thereafter, he felt general fatigue and vertigo, and his serum Na level decreased to 128 mmol/L. Two weeks later, he was referred to our hospital and admitted for a further examination in February 2007. The physical findings upon hospitalization showed a height of 151 cm and a body weight of 47 kg, with a body mass index of 20.6 (Table 1). The patient ex-
hibrated a mild disturbance of consciousness (Glasgow Coma Scale: 14 points). His blood pressure was 141/60 mmHg and his pulse rate was 68 beats/min with a regular rhythm. He had dry mouth and decreased skin turgor. There were no abnormal findings in the chest or abdomen. The neurological findings revealed muscle weakness of the upper and lower extremities. He had no history of chronic vomiting or diarrhea. The laboratory findings revealed a serum Na level of 116 mmol/L, a K level of 2.6 mmol/L and a Cl level of 77 mmol/L (Table 2). Meanwhile, the levels of urinary excretion of Na, K and Cl were increased. The plasma renin activity was 1.9 ng/mL/h, the plasma aldosterone concentration was 24.1 pg/mL and the thyroid function and adrenocorticotropic hormone (ACTH)-cortisol axis were normal. The plasma osmolality was markedly reduced to 226 mmol/kg, while the urinary osmolality was elevated to 585 mmol/kg and the plasma AVP level was 4.7 pg/mL. Brain magnetic resonance imaging was unremarkable. The patient was treated with the cautious infusion of hypotonic saline on the first day of admission due to a mild disturbance of consciousness and severe hyponatremia. He exhibited a state of circulatory volume depletion, and the losartan and hydrochlorothiazide were withdrawn. No other drugs that cause hyponatremia were administered. Seven days later, the serum Na level increased to 132 mmol/L, and the patient became fully alert. He began a normal diet containing 10 g/kg of NaCl. Fifteen days later, he had no symptoms, and his electrolyte levels were normal.

In summary, three patients exhibited hypertension and were administered combination treatment consisting of ARBs and thiazide. Subsequently, they presented with severe hyponatremia and were referred to our hospital. After withdrawing the combined ARB and thiazide therapy, the serum sodium levels became normal (Table 1, 2). At the time of discharge, the blood pressure values were almost normal (systolic blood pressure: 120–140, diastolic blood pressure: 60–80 mmHg); therefore, we did not restart the antihypertensive drugs.

**Discussion**

All three patients presented with severe hyponatremia, although the plasma AVP levels were elevated. The patients were administered a combination of ARBs and thiazide diuretics. The laboratory data showed hyponatremia, decreased uric acid levels and non-suppressible plasma AVP levels, despite the presence of hypo-osmolality. It is evident that the pathological role of an elevated plasma AVP level can be divided into two categories. First, AVP is inappropriately secreted from the posterior pituitary in patients with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and edematous diseases. Second, AVP release occurs in response to a decrease in the circulatory blood volume (4). In the present three cases, skin turgor was reduced and hyponatremia was accompanied by enhanced natriuresis. Such findings indicate that circulatory blood volume depletion stimulates AVP release. The impact of age on AVP secretion may also play an important role in the development of hyponatremia, as the amount of AVP released is greater in the elderly than in younger subjects (5, 6). Thiazide diuretics are widely available in many countries as a first-line drug for treating uncomplicated hypertension. In Japan, elderly individuals have taken a liking to salty food, and there is a high prevalence of salt-sensitive hypertension. Thiazide diuretics are useful for treating salt-sensitive hypertension, as the actions of the diuretic thiazide are linked to natriuresis. Recently, several studies have reported useful effects of treatment with thiazide diuretics (2, 7). A low dose of thiazide administered in combination with either an angiotensin-converting enzyme (ACE) inhibitor or ARB is a beneficial antihypertensive treatment. However, it remains unclear whether the administration of thiazide treatment for hypertension in elderly subjects is beneficial. The randomized, controlled Hypertension in the Very Elderly Trial (HYVET) provided evidence that antihypertensive treatment with indapamide, with or without perindopril, in persons 80 years of age or older is beneficial. That study demonstrated the benefits of antihypertensive therapy in elderly subjects (3). For these reasons, thiazide diuretics are administered in many elderly patients with hypertension. Attention must be paid to hyponatremia as a side effect of thiazide, as the development of thiazide-induced hyponatremia is not rare in elderly subjects. Sharabi et al. reported that both men and women 75 years of age and older are approximately 16 times more likely to develop hyponatremia than those younger than 65 years of age. The patients in this report received an average daily dose of 35 mg of thiazide diuretics. Even when using such a low dosage, there remains the possibility of thiazide-induced hyponatremia in elderly subjects (8-10). Findings of low renin and aldosterone levels and a reduced renal response to aldosterone have been reported in elderly patients (11, 12). In the present three cases, the plasma renin activity was low in spite of a decrease in the circulatory blood volume and the administration of ARBs. We believe that the low level of renin secretion, as well as impaired renal Na management (13, 14), accelerates the development of hyponatremia in elderly subjects. Furthermore, AT1 receptor inhibition induced by ARBs decreases renal tubular sodium reabsorption (15) and aldosterone secretion (16); such factors are also important for advancing disease severity. In case 3, the patient restricted his salt intake due to hypochondria for one year, which may have played a role in increasing the severity of the hyponatremia. Rastogi et al. pointed out that risk factors, such as age, ACE inhibitor use and hypokalemia, are profoundly associated with thiazide-induced hyponatremia (17). Preventing thiazide-induced hyponatremia is important, and carefully monitoring the serum sodium level, providing counseling regarding water intake and administering the lowest possible dosage of thiazide will reduce the risk of the disease (18). Diuretics, especially thiazide, are convenient medications for treating hypertension in combination with ARBs; however, it must be acknowledged...
that thiazide-induced hyponatremia is a pre-existing and recent side effect in elderly subjects.

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

References


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