Prompt Efficacy of Tolvaptan in Treating Hyponatremia of Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) Closely Associated with Rupture of a Gastric Artery Aneurysm

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

Abstract

A 78-year-old man with abdominal pain was diagnosed with a rupture of a gastric artery aneurysm. The serum Na level promptly decreased from 135 to 110 mmol/L within several days. Brain magnetic resonance angiography revealed severe vasoconstriction of the cerebral basilar artery and anterior cerebral artery. There was neither dehydration nor edema. The plasma arginine vasopressin level was 3.3 pg/mL, despite hyposmolality. These findings indicated a diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) derived from severe vasoconstriction of the cerebral arteries. The administration of 7.5 mg of tolvaptan rapidly increased the serum Na level from 123 to 138 mmol/L within the first 24 hours, thereafter continuously maintaining a normal level. Treatment with tolvaptan corrected the patient’s dilutional hyponatremia.

Key words: arginine vasopressin (AVP), gastric artery aneurysm, AVP V2 receptor antagonist, hyponatremia, cerebral artery vasoconstriction

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Introduction

Hyponatremia is a feature of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (1, 2). The causes of SIADH include cancer, central nervous system disorders, intrathoracic disorders and drug administration (3). SIADH is an endocrine disorder; however, its pathological background is based on the pathophysiology of non-endocrine disorders. Hormonogenesis of arginine vasopressin (AVP) is evident in the ectopic production of AVP in cancer patients, as tumor cells per se synthesize and secrete AVP autonomously (4). In other causes of the disorder, the augmented secretion of AVP is derived from the hypothalamic-neurohypophyseal system; thus, its interaction is mediated via neuronal or humoral pathways. However, the relevant signaling pathway has not yet been determined.

The inappropriate secretion of AVP exaggerates water reabsorption in the renal collecting duct in patients with SIADH. When the augmented hydroosmotic action of AVP is inhibited by an AVP V2 receptor antagonist, persistent diuresis reduces excessive water retention and dilutional hyponatremia disappears. We previously reported that mozavaptan (OPC-31260) promptly normalize the serum sodium (Na) levels in experimental SIADH rats exhibiting hyponatremia of less than 120 mmol/L (5). The SALT study provided clinical evidence that tolvaptan normalizes the serum Na levels in SIADH patients (6). Therefore, AVP V2 receptor antagonists are expected to have therapeutic efficacy in treating hyponatremia in patients with SIADH.

In the present study, we report a case of SIADH resulting from an atypical cause and discuss the therapeutic efficacy of tolvaptan in treating hyponatremia.
Case Report

A 78-year-old man developed abdominal pain during his journey and was admitted to a local hospital in the end of June, 2012. He was diagnosed with rupture of a gastric artery aneurysm. The serum Na level was 135 mmol/L at hospitalization. The patient was treated with intravascular coagulation therapy and infusion of physiological saline and/or electrolyte-balanced solution at a volume of 1,500 mL per day. Several days later, the serum Na level profoundly decreased to 110 mmol/L. A diagnosis of SIADH was suspected, and the cause was extensively investigated. Brain magnetic resonance (MR) angiography revealed severe vasoconstriction of the cerebral basilar artery and anterior cerebral artery (Fig. 1A). Brain MR imaging (MRI) depicted leukoencephalopathy (Fig. 2A) in addition to an old cerebral infarct and small subdural hematoma. The patient was referred to Jichi Medical University Saitama Medical Center in the beginning of July, 2012 for a further evaluation. At 77 years of age he had developed diabetes mellitus and was subsequently treated with diet therapy and drug therapy with sitagliptin (50 mg) and gliclazide (20 mg). His current hemoglobin A1c level ranged from 5.8% to 7.2%.

The physical findings on hospitalization included a height of 163 cm, a body weight of 54.4 kg and a body mass index of 20.5. The patient’s blood pressure was 134/87 mmHg without postural changes, his pulse rate was 101 beats/min with a regular rhythm and his body temperature was 37.0°C. There was no dry mouth, and normal skin turgor was observed. There were no abnormal findings in the head, neck, chest or abdomen. No edema was noted in the legs or feet.

Figure 1. Magnetic resonance (MR) angiography performed at (A) the time of gastric artery aneurysm rupture and (B) the time of admission to our hospital. The arrows show vasoconstriction of the cerebral basilar artery and anterior cerebral artery (A).

Figure 2. Brain magnetic resonance imaging depicted leukoencephalopathy following rupture of the gastric artery aneurysm (A). This finding had disappeared upon admission to our hospital (B).
The patient’s ability to maneuver during the finger-nose test was poor.

The laboratory findings were as follows: white blood cell count, 6,080/mm$^3$; red blood cell count, 341×10$^4$/mm$^3$; hemoglobin, 10.5 g/dL; hematocrit, 30.5%; and platelets, 23.3×10$^4$/mm$^3$. The serum electrolyte levels were: Na, 125 mmol/L; potassium, 4.3 mmol/L; and chloride, 95 mmol/L. The patient’s blood chemistry profile showed a blood urea nitrogen level of 10 mg/dL, a serum creatinine level of 0.51 mg/dL, and a uric acid level of 2.5 mg/dL. The plasma osmolality was 253 mmol/kg. The fasting plasma glucose level was 122 mg/dL, the hemoglobin A1c level was 5.8%, the total cholesterol level was 147 mg/dL and the triglyceride level was 58 mg/dL. The plasma cortisol level was 15.8 μg/dL in the morning. The plasma renin activity was 2.1 ng/mL/hr, with a plasma aldosterone level of 70.4 pg/mL. The serum thyroid stimulating hormone (TSH) level was 0.608 μU/mL, the serum free T3 level was 2.32 pg/mL, and the serum free T4 level was 1.45 ng/dL. The plasma brain natriuretic peptide (BNP) level was 28 pg/mL. The plasma AVP level was 3.3 pg/mL, with a plasma osmolality of 253 mmol/kg.

Brain imaging showed no abnormal findings on a skull X-ray film. Brain MRI demonstrated the disappearance of a high signal at the site of an old cerebral infarct and leukoencephalopathy (Fig. 2B), and MR angiography depicted a normal vascular size of the anterior cerebral artery and cerebral basilar artery, which had been severely constricted 20 days earlier at the former hospital (Fig. 1B). There were no abnormal findings on the chest and abdomen X-ray films or chest and abdominal CT scans.

**Clinical course**

Following admission to our hospital, the patient’s hyponatremia and hypoosmolality persisted without edema or dehydration. The patient’s ability to concentrate urine was maintained, with a urinary osmolality of 648 mmol/kg. There were no abnormalities in the kidney or adrenal function. In addition, the serum uric acid level was decreased at 2.5 mg/dL. The plasma AVP level was relatively high at 3.3 pg/mL, despite a plasma osmolality of 253 mmol/kg. These findings again strongly indicated a diagnosis of SIADH.

A featured abnormality in the radiological studies was vascular constriction of the anterior cerebral artery and cerebral basilar artery during rupture of the gastric artery aneurysm at the former hospital. This vascular constriction had resolved 20 days later when reevaluated.

Fig. 3 shows the patient’s clinical course in association with treatment with tolvaptan. The patient was started on water restriction of less than 1,000 mL per day with a high-salt diet. However, the serum Na level remained as low as 123 mmol/L. The patient and his family had received information regarding tolvaptan and requested its use. After obtaining the patient’s agreement, treatment with tolvaptan was started. A dose of 7.5 mg of tolvaptan was orally administered starting in July 2012. The patient’s urine volume promptly increased from 1,200 to 3,500 mL/day, and his body weight inversely decreased from 54.3 to 51.4 kg. A single dose of 7.5 mg of tolvaptan promptly increased the serum Na level by 15 mmol/L in 24 hours. Oral tolvaptan was taken continuously; however, the patient’s urine volume remained at 1,400-2,000 mL/day, values similar to those observed before the administration of tolvaptan. The serum Na level remained in the normal range. After discharge, the tolvaptan therapy was continued. The serum Na level ranged from 137 to 140 mmol/L during the six-month observation period. Tolvaptan was withdrawn in October; however, the serum Na level promptly decreased from 139 to 130 mmol/L within one week. Therefore, oral tolvaptan therapy was restarted. The dose of tolvaptan was reduced to 7.5 mg in September, then to 3.75 mg every other day in the end of October and then finally withdrawn in the end of March.
The patient was admitted to the emergency unit of the former hospital due to severe abdominal pain. Upon hospitalization, the serum Na level was 135 mmol/L. Seven days later, it promptly decreased to 110 mmol/L. The laboratory and physical findings were in concordance with the criteria for SIADH (1). In addition, the plasma AVP level was relatively high compared with the degree of hypoosmolality. The plasma renin activity remained normal, and hypouricemia was observed. Our initial question was why AVP secretion was inappropriately increased independent of the low plasma osmolality. We identified two atypical findings in association with the cause of SIADH. Namely, there was severe cerebral vasoconstriction of the anterior cerebral and basilar arteries with a subdural hematoma. The occupation of the intracranial space by the subdural hematoma was mild, and the hematoma per se did not compress the brain tissue at the initiation of hyponatremia. No dementia, urinary incontinence or gait disturbances were observed. Therefore, we considered the possibility of the subdural hematoma as the cause of SIADH to be low. In contrast, the severe cerebral vasoconstriction may have been closely related to the rupture of the gastric artery aneurysm. A possible mechanism for the development of SIADH in the present patient is as follows. Cerebral vasoconstriction and its related cerebral ischemia may have affected the hormonal regulation of the hypothalamus. Therefore, hypothalamic ischemic changes may have increased the synthesis and release of AVP from the hypothalamo-neurohypophyseal system (Fig. 4). An increased level of plasma AVP augments the hydroosmotic action (V2 action) of AVP in the renal collecting ducts, thus enhancing water reabsorption and impaired water excretion. Therefore, the patient developed dilutional hyponatremia. However, there are no case reports of SIADH similar to that observed in the present case in the literature. We cannot comment on the particular features of the development of SIADH in the present patient; however, it is of value to demonstrate that rupture of the gastric artery aneurysm and subsequent cerebral vasoconstriction caused SIADH. Intracranial disorders are potential causes of SIADH, although the exact mechanisms by which these disorders augment AVP secretion remain undetermined. Because cerebral vasospasms are often observed in patients with subarachnoid hemorrhage, the present findings indicate that cerebral vasoconstriction promotes hypothalamic ischemia and AVP secretion via the hypothalamo-neurohypophyseal system in patients with various intracranial disorders.

The inappropriate secretion of AVP exaggerates water permeability in the renal collecting ducts. In the acute phase, there is an excess of extracellular fluid due to increased water reabsorption, which leads to dilutional hyponatremia. In the steady state, the metabolism of both water and sodium is altered in order to reduce excessive water retention, thereby resulting in euvolemic hyponatremia (7, 8). Tolvaptan is the best drug for treating hyponatremia in patients with SIADH (6) and is currently available in the United States and Europe, although unfortunately not in Japan as of yet. In the present patient, a single dose (7.5 mg) of tolvaptan promptly increased the serum Na level from 123 to 138 mmol/L during the initial 24-hour observation period concomitantly with an increase in urine volume and a decrease in body weight (6, 9). Although the administration of tolvaptan was continued, the urine volume returned to a similar level after day 2 as that observed before the tolvaptan treatment. The serum Na level remained in the normal range for the rest of the observation period. This finding is quite similar to that observed during the observation period in an experimental model of SIADH in rats (5). Hyponatremia less than 120 mmol/L occurred in the SIADH rats receiving the subcutaneous infusion of l-deamino-8-D-arginine vasopressin (DDAVP) and a liquid diet. The successive administration of an AVP V2 receptor antagonist, OPC-31260, once a day normalized the serum Na level concomitantly with urinary dilution for the initial two days only. These findings strongly indicate that the dilutional hyponatremia was derived from increased extracellular fluid in the present patient, a phenomenon that occurs in the acute phase of SIADH. In contrast, tolvaptan continuously produces diluting urine in patients with congestive heart failure (10, 11). We suspect that the urinary diluting action of tolvaptan differs between the causes of impaired water excretion.

In conclusion, we herein presented a case of SIADH that occurred following the rupture of a gastric artery aneurysm. It is possible that cerebral artery vasoconstriction and cerebral ischemia stimulate the hypothalamo-neurohypophyseal system and release of AVP. In this case, the successive administration of tolvaptan rapidly normalized the serum Na level, maintaining it within the normal range during the six-month observation period. The present findings indicate that tolvaptan corrects the dilutional hyponatremia that is in-
duced by atypical SIADH due to the rupture of gastric artery aneurysms.

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

**References**


