A Novel Vasopressin Dual V_{1A}/V_2 Receptor Antagonist, Conivaptan Hydrochloride, Improves Hyponatremia in Rats with Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)

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We investigated the effects of intravenous administration of conivaptan hydrochloride, a dual vasopressin V_{1A} and V_2 receptor antagonist, on blood electrolytes and plasma osmolality in rats with an experimental syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The experimental SIADH rat model was developed by means of continuous administration of arginine vasopressin (AVP) *via* a subcutaneously implanted osmotic mini pump, and hyponatremia was induced by additional water loading. This model possesses similar characteristics to those observed in patients with SIADH, specifically decreases in blood sodium concentration and plasma osmolality. In this experimental model, intravenous administration of conivaptan (0.1, 1 mg/kg) significantly increased blood sodium concentration and plasma osmolality. On the other hand, intravenous administration of furosemide (10 mg/kg) did not increase either blood sodium concentration or plasma osmolality in the SIADH rats. Moreover, furosemide significantly lowered blood potassium concentration. These results show that conivaptan improves hyponatremia in rats with SIADH, supporting the therapeutic potential of conivaptan in treatment of patients with hyponatremia associated with SIADH.

Key words conivaptan; SIADH; hyponatremia; vasopressin V_2 receptor; aquaretic effect; furosemide

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a clinical state in which the secretion of antidiuretic hormone (ADH), also called arginine vasopressin (AVP), is not suppressed appropriately when plasma osmolality falls below the osmotic threshold and may lead to impaired renal water excretion, increased total body water, and hyponatremia.¹⁾ SIADH is associated with a number of underlying clinical conditions, such as malignancy, lung disease, and central nervous system and hormonal disorders.²⁾

AVP is a peptide hormone that is released from the posterior pituitary gland in response to an increase in plasma osmolality and volume depletion. Three classes of specific receptor have been identified in the periphery. The vasopressin V_{1A} receptor, which has been identified in vascular smooth muscle cells, hepatocytes and platelets, and the vasopressin V_{1B} receptor, which is found predominantly in the anterior pituitary, are coupled to the phosphoinositide pathway and elevation of intracellular Ca^{2+} . The vasopressin V_2 receptor, which is located in the kidney and the vascular endothelium, is coupled to the adenylate cyclase pathway, causing an increase in c-AMP.³⁾

AVP elicits a potent water reabsorption effect in the collecting ducts of the kidney *via* the vasopressin V_2 receptors, as well as systemic vasoconstriction *via* the vasopressin V_{1A} receptors.^{4–6)} The facilitation of renal water reabsorption *via* the vasopressin V_2 receptor results in an increase in total body water, which in turn causes a decrease in blood sodium concentration and plasma osmolality. The increased total body water causes inhibition of sodium reabsorption in the proximal tubule *via* inhibition of the renin-angiotensin-aldosterone system, as well as elevation of glomerular filtration rate and facilitation of the secretion of atrial natriuretic peptide (ANP) from the atrium.⁷⁾ These stimuli produce sus-

tained urinary sodium excretion, and result in hyponatremia, the most common electrolyte disorder associated with SIADH.

Clinical manifestations of hyponatremia range from mild symptoms, such as headache, nausea, and vomiting, to severe symptoms, such as disorientation, disturbed consciousness and seizures.⁸⁾ Although the treatment of hyponatremia should be directed at the primary underlying etiology of disorder, this is not always entirely possible. Thus, the general approach to the management of hyponatremia is normalization of blood sodium concentration by the prevention of water retention in the body.⁹⁾

One treatment used for acute severe hyponatremia is the intravenous administration of furosemide concomitantly with hypertonic saline. Diuretics are used in the treatment of chronic hyponatremia, however, resistance to loop diuretics such as furosemide is a common problem in hyponatremia patients.¹⁰⁾ Further, loop diuretics may worsen hyponatremia and induce hypokalemia, a potentially serious electrolyte disorder that can result in the prolongation of QT interval and the subsequent risk of ventricular arrhythmia.

The recent development of non-peptide vasopressin V_2 receptor antagonists^{11,12)} has allowed further understanding of the pathophysiological role of AVP in hyponatremia.¹³⁾ Study results indicate that vasopressin V_2 receptor antagonism may be an effective and rational treatment for hyponatremia associated with SIADH.^{14,15)}

Conivaptan hydrochloride is a novel non-peptide vasopressin receptor antagonist with a high affinity for rat and human vasopressin V_{1A} and V_2 receptors and rather weak affinity for oxytocin receptors.^{16,17)} Conivaptan have been shown to exert a dose-dependent aquaretic effect in several animal models.^{18,19)} However, the question of whether coni-

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vaptan can alleviate the hyponatremia caused by experimental SIADH has not been determined.

In this study, we investigated the effects of intravenous conivaptan and furosemide, a loop diuretic, on blood electrolyte concentration and plasma osmolality in an experimental SIADH rat model.

MATERIALS AND METHODS

Materials Conivaptan hydrochloride was synthesized by Astellas Pharm Inc. (Tokyo, Japan). Conivaptan weighed to the necessary amount, 10% w/v ethanol (special grade; Kanto Chemical Co., Inc.; Tokyo, Japan) was added and stirred, and 30% w/v propylene glycol (Kanto Chemical Co., Inc.) was added to this mixture. After stirring and dissolving well, the pH of the solution was adjusted to approximately 3.3 with an appropriate volume of lactic acid (Wako Pure Chemical Industries, Ltd.; Osaka, Japan), and the resulting solution was used as the 1 mg/kg conivaptan dosing solution. This solution was diluted with distilled water for injection to adjust the volume. The 0.01 and 0.1 mg/kg conivaptan dosing solutions were prepared by diluting the 1 mg/kg dosing solution with vehicle. Furosemide was commercially supplied in ampoules (Hoechst Japan; Tokyo, Japan, 20 mg/2 ml). Each drug was administered intravenously at 1 ml/kg. Sham and control groups received the same volume of vehicle, composed of 10% ethanol, 30% propylene glycol, and 60% distilled water for injection. AVP was commercially purchased (Peptide Institute Inc.; Osaka, Japan).

Preparation of Rat SIADH Model Male Wistar rats weighing 244 to 313 g were used. The SIADH model was prepared by continuous AVP infusion *via* an implanted osmotic mini pump along with oral water loading according to the method reported by Kinter.²⁰ Briefly, rats anesthetized with ether underwent dorsal subcutaneous implantation of an osmotic mini pump (Alzet model 2001; Durect Corp.; CA, U.S.A.) filled with AVP solution. The AVP solution was prepared by dissolving AVP in distilled water to deliver a dose of 3 μ g/d. Sham-operated rats underwent dorsal subcutaneous implantation of an osmotic mini pump filled with distilled water. The experimental protocol is shown in Fig. 1. The day of surgical implantation was defined as Day 1. Water loading (30 ml/kg *p.o.*) was conducted three times (around 9:00, 13:00, 17:00) on Day 2, and once on Day 3 (around 9:00) in both the SIADH and sham-operated rats.

Study Protocols This study consisted of two experiments. In Experiment 1, the SIADH rats were divided into 4 groups of 5–6 animals each following water loading on Day 3 and administered intravenous conivaptan (0.01, 0.1 or 1 mg/kg) or vehicle (1 ml/kg) *via* the left femoral vein under light ether anesthesia (Fig. 1).

In Experiment 2, groups of 4–5 SIADH rats were given intravenous furosemide (10 mg/kg) or vehicle (1 ml/kg) just after water loading on Day 3, as in Experiment 1. Sham-operated rats were given vehicle in both experiments. At 4 h after dosing, blood samples were collected under ether anesthesia to determine sodium, potassium and chloride concentrations in blood by the electrode method with an electrolyte analyzer (Chiron 348; Chiron Diagnostics Corp.; MA, U.S.A.). Plasma samples were obtained by centrifugation of blood at 3000 rpm for 15 min at 4 °C. Plasma osmolality was

Fig. 1. Experimental Protocol

measured by the freezing point depression method using an osmometer (Model 3C2, Advanced Instruments, Inc.; MA, U.S.A.).

Statistical Analysis Data were analyzed using the SAS software (SAS Institute Inc.; NC, U.S.A.). All data are expressed as the mean $\pm$ S.E.M. Analysis between the sham-operated group and the vehicle-treated group (referred to as the control group) in both experiments, and between the control and furosemide-treated groups in Experiment 2, was performed by the unpaired Student's *t*-test. Analysis between the control and conivaptan-treated (0.01, 0.1, 1 mg/kg) groups was performed with Dunnett's multiple range test in Experiment 1. A *p* value of less than 0.05 was considered statistically significant.

Ethical Considerations The protocol for this study was approved by the Animal Ethical Committee of Astellas Pharma Inc.

RESULTS

Effect of Single Intravenous Administration of Conivaptan in SIADH Rats (Experiment 1) The effect of conivaptan on blood electrolytes and plasma osmolality in the SIADH rats at 4 h after dosing is shown in Figs. 2 and 3.

In the control group, blood sodium concentration was markedly decreased (123.2 ± 2.0 mEq/l) compared to that in the sham-operated group (142.4 ± 0.7 mEq/l). Plasma osmolality was 306.6 ± 2.5 mOsm/kg H₂O in the sham-operated group but significantly lower at 273.5 ± 5.1 mOsm/kg H₂O in the control group (Fig. 2). No marked differences in blood potassium concentration were observed (Fig. 3). Blood chloride concentration in the control group was significantly decreased compared with that in the sham-operated group (Table 1).

As shown in Fig. 2, intravenous administration of conivaptan at doses of 0.1 and 1 mg/kg produced a statistically significant increase in blood sodium concentration and plasma osmolality in the SIADH rats. The blood potassium concentration did not change in either the conivaptan 0.1 or 1 mg/kg-treated groups compared with that in the control group (Fig. 3). Blood chloride concentration increased in a dose-dependent fashion in the conivaptan-treated groups (Table 1).

Effect of Single Intravenous Administration of Furosemide in SIADH Rats (Experiment 2) The effect of furosemide on blood electrolytes and plasma osmolality in the SIADH rats at 4 h after dosing is shown in Figs. 4 and 5.

In the control group, blood sodium concentration was significantly decreased (119.8 ± 2.8 mEq/l) compared to that in

Table 1. Effects of Convaptan and Furosemide on the Blood Chloride Concentration in the SIADH Rats

	Sham	Control	Convaptan (mg/kg i.v.)			Furosemide (mg/kg i.v.)
			0.01	0.1	1	10
Cl (mEq/l)						
Experiment 1	106.6±0.2	87.8±1.7**	92.5±3.5	99.2±4.3	104.0±3.6 ^{##}	—
Experiment 2	109.6±2.5	85.8±2.4**	—	—	—	80.3±3.1

Values represent the mean±S.E.M. of 4–6 experiments. Statistical analysis between the sham-operated group and the control group were performed with Student's *t*-test (***p*<0.01). Statistical analysis between the control group and the convaptan-treated groups were performed with Dunnett's multiple test (^{##}*p*<0.01).

Fig. 2. Effects of Intravenous Convaptan (0.01, 0.1, 1 mg/kg) on Blood Sodium Concentration (Upper Panel) and Plasma Osmolality (Lower Panel) in SIADH Rats

Columns with a vertical bar represent the mean±S.E.M. of 5–6 experiments. Statistical analysis between the sham-operated and control groups was performed with Student's *t*-test (^{##}*p*<0.01), and between the control and convaptan-treated groups with Dunnett's multiple test (**p*<0.05, ***p*<0.01).

Fig. 3. Effect of Intravenous Convaptan (0.01, 0.1, 1 mg/kg) on Blood Potassium Concentration in SIADH Rats

Columns with vertical bars represent the mean±S.E.M. of 5–6 experiments.

the sham-operated group (144.2 ± 0.9 mEq/l), as was plasma osmolality (246.8 ± 6.8 mOsm/kg H_2O in the control group versus 292.8 ± 1.4 mOsm/kg H_2O in the sham-operated

Fig. 4. Effects of Intravenous Furosemide (10 mg/kg) on Blood Sodium Concentration (Upper Panel) and Plasma Osmolality (Lower Panel) in SIADH Rats.

Columns with vertical bars represent the mean±S.E.M. of 4–5 experiments. Statistical analysis between the sham-operated and control groups was performed with Student's *t*-test (^{##}*p*<0.01).

Fig. 5. Effect of Intravenous Furosemide (10 mg/kg) on Blood Potassium Concentration in the SIADH Rats

Columns with vertical bars represent the mean±S.E.M. of 4–5 experiments. Statistical analysis between the control and furosemide-treated groups was performed with Student's *t*-test (***p*<0.01).

group) (Fig. 4). Blood potassium concentration remained unchanged in the control group compared with that in the sham-operated group (Fig. 5), whereas blood chloride concentration was significantly reduced (Table 1).

Intravenous furosemide (10 mg/kg) did not increase in either blood sodium concentration (119.8 ± 4.5 mEq/l) or plasma osmolality (253.3 ± 8.7 mOsm/kg) in the SIADH rats compared to the vehicle-treated SIADH rats (Fig. 4). Blood potassium concentration was significantly decreased in the furosemide-treated group (3.65 ± 0.02 mEq/l) compared with the control group (4.18 ± 0.13 mEq/l) (Fig. 5), whereas blood chloride concentration showed no increase (Table 1).

DISCUSSION

In this study, we investigated the effect of intravenous conivaptan in SIADH rats, and demonstrated that conivaptan increased blood sodium concentration and plasma osmolality in this animal model. In contrast, furosemide did not significantly increase blood sodium concentration or plasma osmolality, but did induce hypokalemia in SIADH rats. These findings indicate that conivaptan has therapeutic potential for the effective treatment of hyponatremia associated with SIADH.

SIADH is a condition in which the plasma AVP level is not appropriately suppressed despite of hypoosmolality. The vasopressin V_2 receptor plays a prominent role in the regulation of water homeostasis. Therefore, the effect of sustained high level of AVP *via* the vasopressin V_2 receptor are closely implicated in water retaining diseases, including hyponatremia, renal disease, cirrhosis and edema.²¹⁾ We produced SIADH rats by means of continuous administration of AVP *via* a subcutaneously implanted osmotic mini pump. The SIADH rat model, which exhibits a dilutional reduction in blood sodium concentration due to water retention caused by continuous administration of AVP, was originally developed by Kinter.²⁰⁾ In Experiments 1 and 2, blood sodium concentration in SIADH rats of the control group significantly fell to 123 and 120 mEq/l, respectively, compared to the sham-operated groups (142, 144 mEq/l, respectively). Given that hyponatremia is clinically defined as a serum sodium level less than 136 mEq/l,²²⁾ these findings indicate that continuous infusion of AVP and additional forced water loadings for 3 d promptly produced hyponatremia in the SIADH rats.

SIADH is associated with abnormal water retention mediated by inappropriate AVP release despite hypotonicity.²³⁾ Since excess AVP continuously exerts a potent water retention effect *via* vasopressin V_2 receptors in the distal renal tubule, dilutional hyponatremia can be induced in SIADH rats. In clinical practice, hyponatremia is a common electrolyte disorder that is frequently undertreated. Although the pathophysiological process of hyponatremia is complex, SIADH is a common etiologic factor.

In the present study, intravenous conivaptan significantly increased blood sodium concentration and plasma osmolality in the SIADH rats 4 h after dosing. No marked change in blood potassium concentration was seen in the conivaptan treated groups. Conivaptan has been shown to inhibit the binding of radiolabeled AVP to the vasopressin V_2 receptor in a competitive manner.^{16,17)} Additionally intravenous conivaptan has been reported to increase urine volume in a dose-

dependent manner without an increase in urine electrolytes in rats and dogs.^{16,19,24)} In our study, we confirmed a dose-dependent aquaretic effect of intravenous conivaptan (0.01, 0.1, 1 mg/kg) (data not shown) in an SIADH rat model. We therefore consider that the increase in water excretion caused by vasopressin V_2 receptor blockade is closely related to the increase in blood sodium concentration and plasma osmolality in these SIADH rats. This finding is supported by clinical evidence in patients with SIADH. Patients treated with intravenous OPC-31260, a vasopressin V_2 receptor antagonist, demonstrated an increase in urine volume and decreased urine osmolality during the initial 4 h after dosing, resulting in a significant increase in serum sodium level.¹⁵⁾

Song *et al.* reported a slight increase in mean blood pressure in desmopressin (1-deamino-[8-D-arginine]-vasopressin)-infused rats which also showed water retention and hyponatremia.²⁵⁾ Desmopressin is an AVP analogue which shows a strong antidiuretic effect but less potent vasoconstrictive effect because of its agonistic effect on the vasopressin V_2 receptor and antagonistic effect on the vasopressin V_{1A} receptor.²⁶⁾ Volume expansion may therefore contribute to the increase in mean blood pressure in desmopressin-infused rats. In the present study, blood pressure was not determined in the SIADH rats, although it was presumed that blood pressure rose on continuous infusion of AVP which exerts vasoconstrictive effect *via* the vasopressin V_{1A} receptor in addition to water retention *via* the vasopressin V_2 receptor. Clinical reports of elevation in blood pressure in association with SIADH also exist.^{27,28)} Conivaptan is a combined V_{1A}/V_2 receptor antagonist^{16,17)} and the use of the dual antagonist has the theoretical advantage of reducing blood pressure elevated by excessive AVP.

Intravenous administration of conivaptan was shown to improve hyponatremia in a dose-dependent fashion in SIADH rats. The fundamental principle of treatment for hyponatremia is normalization of the decreased blood sodium concentration. However, the optimal rate of blood sodium correction in patients with chronic hyponatremia remain controversial owing to the risk of developing brain damage, such as osmotic demyelolysis, if rapid correction of blood sodium concentration occurs in patients who have already undergone a cerebral adaptation.²⁹⁾ As a general, the decreased blood sodium concentration in patients with chronic or severe hyponatremia must be normalized by limiting the correction rate.³⁰⁾ An intravenous formulation of conivaptan allows the flexible adjustment of doses and may be useful to the management of patients with chronic hyponatremia, in whom blood sodium levels should be corrected with caution. Even if so, it is recommended that the blood sodium levels and neurologic status in the patients treated with intravenous conivaptan should be closely monitored to avoid overcorrection.

Furosemide is commonly prescribed when immediate treatment is required in patients with acute developed hyponatremia, who are at high risk of cerebral oedema, cerebral herniation.³¹⁾ In the present study, intravenous furosemide at a dose of 10 mg/kg had no effect on either blood sodium concentration or plasma osmolality in the SIADH model. The dosage of furosemide was confirmed to increase urine volume in the SIADH rats to a closely similar degree to intravenous conivaptan at 0.1 mg/kg, and to increase urinary

sodium excretion (data not shown). Therefore, this diuretic might not directly address a hyponatremia induced by the effect of excess AVP. The excessive natriuretic effect of these diuretics may further decrease plasma sodium concentration, resulting in an imbalance in plasma electrolytes. In addition, it is reported that treatment by long-term administration of loop diuretics enhances water retention, resulting from water reabsorption in the kidney collecting duct stimulated by enhanced physiological AVP secretion.³²⁾ Further, furosemide in the present SIADH rats was shown to simultaneously decrease blood potassium concentration. Given that furosemide facilitates sodium and potassium excretion in the renal tubule,³³⁾ the potential may exist for hypokalemia as well as hyponatremia. It has been demonstrated that hypokalemia increases susceptibility of the heart to ventricular arrhythmia in experimental studies.^{34,35)} Particularly in the diseased heart, hypokalemia might be a risk factor for secondary prolongation of QT interval and consequent life-threatening cardiac arrhythmia.^{36–38)} Considered together, these findings may offer a warning that the use of furosemide in patients with hyponatremia resulting from persistently high AVP levels theoretically seems inappropriate.

In conclusion, the present study demonstrated that conivaptan improves hyponatremia in the rat SIADH model. In contrast, furosemide was not only unable to correct hyponatremia in these rats, but additionally induced hypokalemia. These results indicate that the vasopressin antagonist conivaptan may be a specific and appropriate treatment option for patients with hyponatremia secondary to SIADH.

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