

## Forum Minireview

**New Topics in Vasopressin Receptors and Approach to Novel Drugs:  
Research and Development of Conivaptan Hydrochloride (YM087),  
a Drug for the Treatment of Hyponatremia**Yukinori Arai<sup>1,\*</sup>, Akira Fujimori<sup>1</sup>, Masao Sasamata<sup>1</sup>, and Keiji Miyata<sup>1</sup><sup>1</sup>Applied Pharmacology Research Laboratories, Drug Discovery Research, Astellas Pharma Inc.,  
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**Abstract.** Hyponatremia is the most common electrolyte disorder in hospitalized patients and is associated with the risk of intractable seizures and death. The effectiveness of conventional therapies for hyponatremia is inconsistent, and the rapid correction of plasma sodium levels is thought to result in the occurrence of neurological complications. Arginine vasopressin (AVP) is the primary regulator of renal electrolyte-free water reabsorption via AVP-receptor type 2 (V2-R), and inappropriate or excessive AVP secretion independent of serum osmolality frequently causes excessive water retention, which is the etiological basis of hyponatremia. Therefore, the use of V2-R antagonists as anti-hyponatremic drugs in the clinical setting is anticipated to be reliable and safe. Conivaptan hydrochloride (YM087) is a novel dual AVP-R antagonist for AVP-R types 1a (V1a) and V2-R. In vitro studies have shown that it possesses high affinity for V1a-R and V2-R without any species differences. It also potently inhibited AVP-induced intracellular signaling through human V2 and V1a receptors with no agonistic activity. Conivaptan hydrochloride improved the plasma sodium concentration and plasma osmolality in hyponatremic rats, and its effectiveness was demonstrated in hyponatremic patients. This drug has been approved for use in the United States, which will bring relief to patients with hyponatremia.

**Keywords:** YM087, conivaptan hydrochloride, arginine vasopressin,  
arginine vasopressin (AVP) receptor antagonist, hyponatremia

**Introduction**

Hyponatremia, defined as a plasma sodium concentration less than 130 to 135 mEq/L (1, 2), is the most common disorder associated with fluid and electrolyte imbalance encountered in hospitalized patients (3). Based on its principal causes, hyponatremia can be classified as hypovolemia, euvoolemia, and hypervolemia (4). Hyponatremia is caused by an excess of total body water (TBW) relative to total body sodium (TBNa). Hypovolemic hyponatremia, which can result from severe diarrhea, prolonged vomiting, and so on, is characterized by deficiencies in both TBW and TBNa, but sodium depletion is disproportionally greater than

the loss in TBW. This consequently leads to a significant decrease in extracellular fluid (ECF) volume. Euvolemic hyponatremia is a condition in which TBW increases, but there is no significant change in TBNa, with even less of a change in ECF volume. Euvolemic hyponatremia is commonly caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Hypervolemic hyponatremia is characterized by increases in both TBW and TBNa with an accompanying increase in ECF volume; however, the increase in TBW is greater than that in TBNa. This type of hyponatremia occurs mainly with congestive heart failure (CHF), cirrhosis, or nephrosis (4).

Arginine vasopressin (AVP), also known as anti-diuretic hormone, regulates renal electrolyte-free water reabsorption and blood volume to maintain body fluid osmolality stringently within the narrow normal range and maintain systemic perfusion pressure (5, 6). AVP is

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synthesized in the magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus and is stored in the posterior pituitary. Secretion into systemic circulation is primarily regulated by serum osmolality and blood pressure (5, 7). Changes in serum osmolality are detected by osmoreceptors located in the hypothalamus, while changes in blood pressure are detected by pressure-sensitive receptors (baroreceptors) located in the carotid artery, aortic arch, and left atrium. Because AVP secretion is far more sensitive to small changes in serum osmolality than to changes in blood volume (7), inappropriate AVP secretion independent of serum osmolality (nonosmotic secretion) frequently causes excessive free water retention, resulting in reduced serum sodium concentrations and edema (8). This excess nonosmotic secretion of AVP is thought to be central to the pathophysiology of hyponatremia; therefore, inhibition of excessive AVP secretion or action is a theoretically reasonable therapeutic strategy for the treatment of such disorders. The intravenous formulation of conivaptan hydrochloride (YM087), a dual AVP-receptor type 1a (V1a-R) and type 2 (V2-R) antagonist, has been recently approved in the USA for use in hospitalized patients with euvolemic and hypervolemic hyponatremia. This review summarizes the importance of treating hyponatremia, preclinical pharmacology data of conivaptan hydrochloride, and its effectiveness in hyponatremic patients.

### Conventional treatment for hyponatremia

Symptoms of hyponatremia are primarily neurological and include nausea, vomiting, headache, irritability, and lethargy, which are due to cerebral edema caused by a shift of free water from the vascular space into the interstitial space (2). Most cases of hyponatremia are usually mild and asymptomatic; however acute or severe (less than 120 mEq/L) hyponatremia often causes seizures, coma, and even death (2). Hyponatremia is commonly divided into three types based on severity and/or urgency of treatment: acute and chronic symptomatic and chronic asymptomatic hyponatremia (9). The most serious type of hyponatremia is acute, followed by chronic symptomatic (10). Rapid correction of the serum sodium concentration in severely hyponatremic patients is needed to reduce the risk of more severe neurological complications (11). However, it is important to note that the rapid or excessive correction of hyponatremia itself has the potential to cause osmotic demyelination syndrome and pontine myelinolysis, which is thought to result from an acute shift of free water from the interstitial to the vascular space (9). In consideration of the risks of hyponatremia- or sodium correction-derived

neurological complications, therapeutic strategies commonly depend on the type of hyponatremia to be treated. Symptomatic hyponatremia for which neurological signs are apparent generally require immediate and aggressive treatment, whereas asymptomatic hyponatremia can be managed with slower-acting therapies (9).

Current treatment options for hyponatremia include fluid restriction and administration of hypertonic saline solution, either alone or with loop diuretics (9). For patients with chronic asymptomatic hyponatremia the predominantly used therapy is fluid intake restriction; however there are some limitations, including reduced effectiveness in patients with SIADH, which is compounded by low compliance due to thirst. The use of hypertonic saline solution, which is often the therapy of choice for symptomatic hyponatremia, is difficult for patients with chronic congestive heart failure and, as described above, because it is difficult to manage the rate of serum sodium correction. In addition, hypertonic saline solution is poorly tolerated by patients with advanced CHF or overt congestion (9). Thus, no reliably effective and safe therapy is currently available for hyponatremic disorders; therefore, the development of an anti-hyponatremic drug possessing these qualities is highly desirable.

### Research and development of conivaptan hydrochloride

V2-R antagonists directly inhibit nonosmotically secreted AVP, which causes excessive free water retention; therefore this type of antagonist is thought to be reasonable as an approach for the treatment of hyponatremia. Attempts to create these antagonists have been made since the late 1980s. Initial research focused on a peptide V2-R antagonist; however, their clinical utility was limited due to either agonistic activity, poor oral bioavailability, or a short-term half-life in humans (12, 13). Thereafter, developmental research shifted to the identification of nonpeptide AVP-R antagonists via a random screening method, which led to the creation of non-peptide type AVP-R antagonists in the early 1990s (14, 15). Since 1991, our strategic concept has been to screen for a novel AVP antagonist that has more potent V2-R antagonistic activity, but does not show any species differences or AVP-R agonistic activity. In addition, we attempted to find an AVP-R antagonist possessing activity for V1a-R as well as V2-R because V2-R antagonists have been shown to reflexively increase plasma AVP levels when administered to both animals (16, 17) and humans (18). The V2-R antagonists might then stimulate non-desired V1a receptor-derived effects, including vasoconstriction and platelet aggrega-

**Table 1.** In vitro pharmacological properties of conivaptan

		Conivaptan	OPC-21268	SKF-100273	OPC-31260	AVP
AVP receptor subtype binding ( $K_i$ , nM)						
Rat	V1a	$0.51 \pm 0.11$	$21.5 \pm 4.4$	$1.34 \pm 1.02$	$161 \pm 60$	$1.03 \pm 0.29$
	V1b	>10000	>10000	$35.4 \pm 4.4$	>10000	$0.22 \pm 0.03$
	V2	$2.84 \pm 1.40$	>10000	$69.9 \pm 23.1$	$39.4 \pm 14.1$	$3.14 \pm 1.22$
Human	V1a	$4.45 \pm 1.20$	>10000	$0.63 \pm 0.19$	$46.5 \pm 6.6$	$0.46 \pm 0.12$
	V1b	>10000	>10000	$104 \pm 15$	>10000	$0.34 \pm 0.03$
	V2	$1.81 \pm 0.18$	>10000	$119 \pm 34$	$23.8 \pm 4.7$	$3.49 \pm 0.88$
Effects on AVP-induced intracellular signaling ( $IC_{50}$ , nM)						
	V1a	$1.05 (0.76 - 1.44)$	>10000	$0.3 (0.27 - 0.35)$	$78.1 (72.0 - 84.6)$	NT
	V1b	>10000	>10000	$471 (408 - 544)$	>10000	NT
	V2	$1.67 (1.22 - 2.30)$	>10000	$176 (133 - 233)$	$13.8 (10.9 - 17.5)$	NT

Values represent the mean  $\pm$  S.E.M. of 3–11 experiments for the AVP-receptor binding study, and the mean (95% confidence intervals in parentheses) of 3–8 experiments for the intracellular signaling study. The plasma membrane fraction from rat liver, pituitary, or renal medulla was used to assess the binding affinity for V1a, V1b, or V2 receptors, respectively. With respect to the binding studies on human AVP receptors, membrane fractions from Chinese hamster ovary (CHO) cells expressing recombinant human AVP-receptor subtypes were used. Intracellular  $Ca^{2+}$  elevation or cyclic AMP production induced using AVP at 10 nM was measured using CHO cells expressing human AVP-receptor subtypes to assess the inhibitory effects of AVP antagonists on intracellular signaling for V1a and V1b receptors or the V<sub>2</sub> receptor, respectively. OPC-21268 is a nonpeptide V1a-receptor-selective antagonist; OPC-31260, a nonpeptide V2-receptor-selective antagonist; SKF-100273, a peptide V1-receptor-selective antagonist; AVP: arginine vasopressin;  $K_i$ : inhibitory constant,  $IC_{50}$ : concentration required to induce 50% inhibition; NT: not tested.

tion (19, 20), which might be especially be important in hyponatremic patients with CHF. Our novel V2-R antagonist, conivaptan hydrochloride, possesses these desired characteristics.

### Preclinical pharmacological study

#### *In vitro pharmacological properties*

The results of the in vitro studies are summarized in Table 1. The affinity and selectivity of conivaptan hydrochloride for rat and human AVP-R subtypes were investigated for comparison with those of known AVP-R antagonists (21, 22). Conivaptan hydrochloride concentration-dependently inhibited the binding of [<sup>3</sup>H]AVP to rat V1a-R and V2-R, but not to V1b-R. Comparison of the inhibitory constants ( $K_i$ ) showed that the affinity of conivaptan hydrochloride for the rat V1a receptor was about 43 times higher than that of OPC-21268 (V1a-R antagonist), and its affinity for the rat V2 receptor was about 14 times higher than that of OPC-31260 (V2-R antagonist). With respect to human AVP-R subtypes, conivaptan hydrochloride exhibited similar selectivity for both human V1a-R and V2-R as well as nanomolar affinity for both AVP-Rs; the AVP-Rs had an affinity for human V1a-R and V2-R about 10 and 13 times higher than that of OPC-31260, respectively. Next, we tested whether conivaptan hydrochloride actually inhibits functional intracellular signal transduction through V1a-R and V2-R. Conivaptan hydrochloride

was found to potently and concentration-dependently inhibit AVP (10 nM)-evoked intracellular  $Ca^{2+}$  elevation via V1a-R. As in the receptor binding study, conivaptan hydrochloride had no effect on the elevation in intracellular  $Ca^{2+}$  via human V1b-R. Intracellular cyclic AMP production via human V2-R was also potently inhibited by the drug, the potency of which was 8 times greater than that of OPC-31260. Conivaptan hydrochloride had no agonistic effect on human V1a-R or V2-R at concentrations up to 10  $\mu$ M.

#### *In vivo AVP-R antagonistic action*

To confirm the in vivo AVP-R antagonistic activity of intravenously injected conivaptan hydrochloride, we tested the inhibitory effects of the drug on pressor response induced by AVP and water diuresis, known as the aquaretic effect, after water depletion (Table 2). Conivaptan hydrochloride (0.003 to 0.03 mg/kg, i.v.) inhibited the AVP-induced increase in diastolic blood pressure in pithed rats in a dose-dependent manner. OPC-21268 had the same suppressive effect on AVP, but a comparison of the  $ID_{50}$  values of both antagonists showed that OPC-21268's potency was 19 times weaker than that of conivaptan hydrochloride. The aquaretic effect of conivaptan hydrochloride after intravenous administration was studied in conscious rats deprived of drinking water for 16–20 h to stimulate endogenous AVP secretion. Intravenous administration of conivaptan hydrochloride (0.01 to 0.3 mg/kg) produced a dose-

**Table 2.** In vivo AVP receptor antagonistic activities of conivaptan

	Conivaptan	OPC-21268	OPC-31260
V1a antagonistic activity (ID <sub>50</sub> ; mg/kg, i.v.)			
	0.014 (0.0093 – 0.020)	0.26 (0.16 – 0.41)	NT
V2 antagonistic activity (ED <sub>3</sub> ; mg/kg, i.v.)			
	0.028 (0.021 – 0.036)	NT	2.1 (1.8 – 2.4)

Values represent the mean (95% confidence limits in parentheses) of 4 experiments for the V1a-receptor antagonism study and 17–20 experiments for the V2-receptor antagonism study. To assess the in vivo V1a-receptor antagonistic activities of the antagonists, pithe rats anesthetized using sodium pentobarbital were given AVP (30 mU/kg, i.v.), and the change in the diastolic blood pressure value was taken as 100%. The antagonists were administered intravenously in increasing doses to determine the dose causing 50% inhibition of the pressor response to AVP using the linear regression method. With regard to the in vivo V2-receptor antagonistic activity of the antagonists, urine was collected for 2 h after intravenous drug administration to water-deprived rats, followed by measurement of urine flow and urine osmolality. The ED<sub>3</sub> value, the dose required to increase urine flow to 3 mL during the first 2 h after drug administration, was calculated using linear regression.

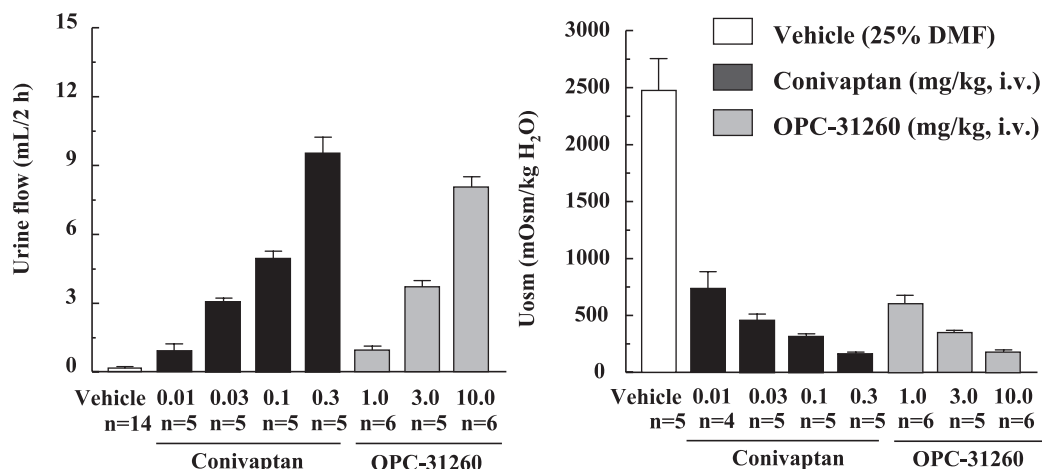
dependent increase in urine flow and decrease in urine osmolality in water deprived conscious rats (Fig. 1). The potency of conivaptan hydrochloride was 75 times greater than that of OPC-31260. Conivaptan hydrochloride (0.3 mg/kg) decreased the urine osmolality to below 290 mOsm/kg H<sub>2</sub>O, indicating that the antagonistic action of the drug against endogenous AVP resulted in urine dilution.

#### Effect on the hyponatremic model

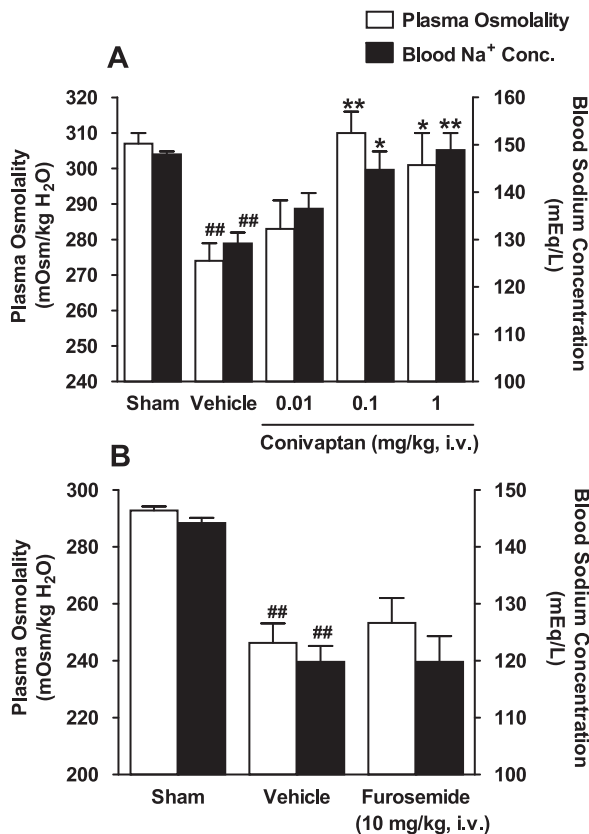
Among the three types of hyponatremia, the applica-

tion of V2-R antagonists is appropriate for the euvoletic and hypervolemic types. Hypovolemic hyponatremia is associated with significant decreases in ECF volume, which results from the excretion of body water to the outside of the body. Under such conditions, endogenous AVP plays a critical role in the maintenance of systemic perfusion. Therefore, the application of V2-R antagonists would break the compensatory system and lead to exacerbated hypotension in hypovolemic patients. Despite the hypotonicity caused by SIADH, the most common cause of hyponatremia (23), AVP secretion is not fully suppressed due to disorganized AVP production by cancer cells or regulatory dysfunction due to brain injury (24). In CHF, reduced arterial pressure caused by dysfunction of the left ventricle stimulates AVP secretion via baroreceptors (7, 25). The mechanism behind the nonosmotic AVP secretion seen with cirrhosis is thought to be arterial underfilling resulting from the vasodilation of splanchnic arterioles caused by portal hypertension (26). Thus, excess elevation of serum AVP is a key etiologic factor for euvoletic and hypervolemic hyponatremia. Hyponatremia was developed in rats after continuous administration of AVP through an intraperitoneally implanted osmotic minipump, along with oral water loading (27).

Compared to the sham rats, the hyponatremic rats had lower plasma sodium concentrations and osmolality values (Fig. 2), which are characteristic signs consistent with symptoms observed in patients with SIADH. Intravenously administered conivaptan hydrochloride dose-dependently and significantly increased the plasma sodium concentration, accompanied by an improvement in the reduced plasma osmolality. Intravenous administration of furosemide at a dose of 10 mg/kg did not



**Fig. 1.** In vivo V2-receptor antagonistic activity. Rats were deprived of drinking water for 16–20 h to stimulate endogenous AVP secretion. After intravenous administration of V2-R antagonist, urine was collected for 2 h, after which urine flow and urine osmolality were measured. DMF is dimethylformamide. n indicates the number of rats.



**Fig. 2.** Effects of conivaptan hydrochloride (A) and furosemide (B) on plasma osmolality and the blood sodium level in SIADH rats. Columns represent the mean  $\pm$  S.E.M. of 4–6 experiments. SIADH rats were developed by means of continuous administration of AVP (3  $\mu$ g/day) via a subcutaneously implanted osmotic mini-pump and oral water loading. Urine was collected for 4 h after intravenous drug administration, followed by measurement of plasma osmolality and blood sodium concentration. SIADH: syndrome of inappropriate secretion of antidiuretic hormone. <sup>##</sup> $P < 0.01$  vs the sham group using the unpaired two-tailed Student's *t*-test. <sup>\*</sup> $P < 0.05$ , <sup>\*\*</sup> $P < 0.01$  vs the vehicle-treated group using Dunnett's multiple test.

improve the decreases in the plasma sodium concentration or osmolality. Conivaptan hydrochloride had no effect on plasma potassium concentration, but furosemide significantly lowered it. Diuretics are used as a first line therapy for patients with CHF, and loop diuretics, such as furosemide, are known to suppress the reabsorption of electrolytes in the proximal renal tubules. Therefore, furosemide could cause a plasma electrolyte imbalance, thereby inducing hypokalemia-related arrhythmia in patients with CHF (28, 29). These data suggest that the V<sub>2</sub>-R antagonist is the appropriate therapeutic agent for treatment of hypervolemic hyponatremic patients with CHF.

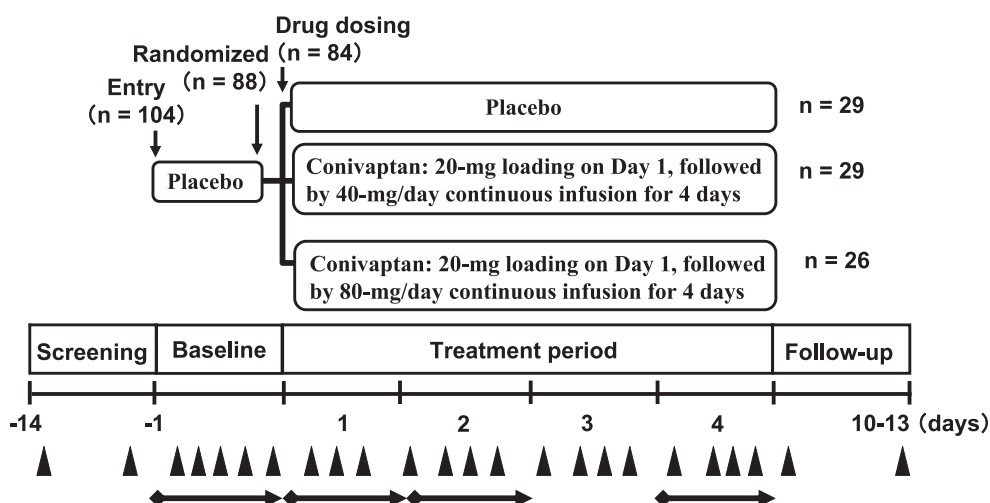
### Clinical study results

The phase 3 study was conducted to assess the

efficacy and tolerability of conivaptan hydrochloride (40 and 80 mg/kg per day) in 84 euvolemic or hypervolemic hyponatremia patients 18 years of age or older with serum sodium concentrations between 115 and 130 mEq/L, in a multicenter, double-blind, and placebo-controlled manner (30). The outline of the study design is shown in Fig. 3. Of the 104 patients who entered the placebo baseline period, 88 were randomly assigned to 3 groups, and 84 received intravenous treatment with the placebo or conivaptan at 40 or 80 mg/day. The primary efficacy endpoint was the change in the serum sodium level from the baseline during the course of treatment, which was measured by the baseline-adjusted area under the serum sodium level–time curve (AUC) throughout treatment. The secondary endpoints included 1) the time from the first dose until an increase of at least 4 mEq/L over the serum sodium level baseline; 2) the total time from the first dose until the end of treatment, at which time patients had a serum sodium level of at least 4 mEq/L higher than that observed at the baseline; 3) the change in the serum sodium level from the baseline until the end of treatment; and 4) the number of patients for which an increase in the serum sodium level of at least 6 mEq/L from the baseline or a normal serum sodium level (at least 135 mEq/L). In addition to safety and tolerability, the rate and extent of the serum sodium level were also assessed.

The efficacy of conivaptan hydrochloride on study endpoints is shown in Table 3. Conivaptan hydrochloride at 40 and 80 mg/day induced significantly greater mean increases in the baseline-adjusted serum sodium AUC than the placebo throughout the study; however, the difference between the 40 mg/kg– and 80 mg/day–conivaptan treatments was not statistically significant. Compared to treatment with placebo, conivaptan hydrochloride significantly improved secondary efficacy parameters. It also decreased urine osmolality and increased plasma osmolality, which caused the free water clearance values to change from negative to positive. These findings demonstrated that conivaptan hydrochloride exhibited an aquaretic effect in humans as well.

Drug-related adverse events were observed in 55.2% and 65.4% of patients given conivaptan hydrochloride at 40 and 80 mg/day, respectively (30). The following are the most common adverse events noted for the placebo, 40 mg/day dose, and 80 mg/day dose (rate of incidence, respectively): infusion-site reactions (6.9%, 24.1%, and 30.8%), hypotension (6.9%, 13.8%, and 19.2%), postural hypotension (0%, 13.8%, and 3.8%), pyrexia (0%, 10.3%, and 7.7%), and hyperkalemia (3.4%, 0%, and 11.5%). The pyrexia seemed to be associated with the infusion-site reactions, and the transient hypotension



**Fig. 3.** Outline of study design for the Phase III clinical trial. During the 14-day screening period, eligible patients who met the inclusion criteria were chosen. These patients were randomized and assigned to one of three arms after measurement of their baseline values, including serum sodium and serum and urine electrolytes, under administration of the placebo solution in a single-blind placebo baseline phase. Conivaptan hydrochloride was intravenously infused at a dose of 20 mg in 30 min on Day 1, followed by continuous infusion of 40 mg/day or 80 mg/kg over the next 4 days. Arrowheads indicate plasma sodium concentration measurement time points; long arrow: urine collection, n: number of patients.

**Table 3.** Efficacy outcomes of treatment with intravenous conivaptan hydrochloride

Study endpoints	Placebo	Conivaptan	
	(n = 29)	40 mg/day (n = 29)	80 mg/day (n = 26)
<b>Primary efficacy</b>			
Change in baseline adjusted serum sodium AUC, LS mean $\pm$ S.E.M., mEq $\cdot$ h/L	12.9 $\pm$ 61.2	490.9 $\pm$ 56.8*	716.6 $\pm$ 60.4*
<b>Secondary efficacy</b>			
Time from first dose to an increase in serum $[\text{Na}^+] \geq 4$ mEq/L from baseline, median (95% CI), h	NE	23.7 (10.0, 24.0)*	23.4 (6.0, 24.0)*
Total time during treatment phase that patients had serum $[\text{Na}^+] \geq 4$ mEq/L above baseline, LS mean $\pm$ S.E.M., h	14.2 $\pm$ 5.25	53.2 $\pm$ 5.17*	72.7 $\pm$ 5.43*
Change in serum $[\text{Na}^+]$ from baseline to end of treatment, LS mean $\pm$ S.E.M., mEq/L	0.8 $\pm$ 0.80	6.3 $\pm$ 0.74*	9.4 $\pm$ 0.79*
Patients with an increase in serum $[\text{Na}^+] \geq 6$ mEq/L or a serum $[\text{Na}^+] \geq 135$ mEq/L	6 (20.7%)	20 (69.0%)*	23 (88.5%)*

AUC indicates the area under the serum sodium level vs time curve from the beginning to the end of treatment, CI: confidence interval, NE: not estimated, LS: least squares. \* $P < 0.001$  vs the placebo group using Dunnett's two-sided multiple test. This table is reprinted from Ref. 30 and is partly modified from the original version. Permission to use this reprint has been granted by the copyright owner, S. Karger AG, Basel.

was thought to be due to the reduction in ECF volume. No patient given conivaptan hydrochloride discontinued, required medication, or had complications due to hypotension. Thus, conivaptan hydrochloride-related adverse events were observed, but their degrees of severity were low; therefore, the drug was thought to be generally well tolerated. There were 4 patients (2 patients in each group given conivaptan hydrochloride) who experienced an excessively rapid correction of the serum sodium level (at 40 mg/day: a 13-mEq/L increase after 24 h and an 8-mEq/L increase within 4 h of initiating treatment; at

80 mg/day: a 25-mEq/L increase after 24 h and a 12-mEq/L increase within 24 h). For these patients, the drug was either discontinued or the drug infusion was adjusted to change the sodium correction rate. There was no apparent onset of neurological adverse events caused by this rapid increase in serum sodium. These clinical data demonstrate that conivaptan hydrochloride was an effective, well-tolerated, and safe drug for the treatment of hyponatremic patients with euolemia or hypervolemia.



## Conclusions

Nonpeptide V2-R antagonists are expected to be applicable to the clinical setting for treatment of hyponatremia. The preclinical pharmacology data showed that conivaptan hydrochloride possesses potent V2-R antagonistic action, but not with species variability or receptor-agonist potential. This was confirmed in vivo in rats; after dosing with conivaptan hydrochloride, urine flow increased and urine osmolality decreased. In addition, in hyponatremic rats, conivaptan hydrochloride effectively corrected plasma sodium levels and osmolality to the normal range without affecting plasma potassium levels. The efficacy and safety of conivaptan hydrochloride was confirmed in hyponatremic patients as well. Based on these data, conivaptan hydrochloride has been approved as the first drug in its class in the USA for treatment of euvoletic and hypervolemic hyponatremia. We hope that the clinical use of conivaptan hydrochloride brings benefits to patients suffering from hyponatremia.

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