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European Journal of Pharmacology 507 (2005) 145–151

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Intravenous administration of conivaptan hydrochloride improves cardiac hemodynamics in rats with myocardial infarction-induced congestive heart failure

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Received 30 August 2004; received in revised form 2 November 2004; accepted 12 November 2004
Available online 1 January 2005

Abstract

We investigated the effects of intravenously administered conivaptan hydrochloride, a dual vasopressin V_{1A} and V_2 receptor antagonist, on cardiac function in rats with congestive heart failure following myocardial infarction, and compared results with those for the selective vasopressin V_2 receptor antagonist SR121463A. Rats were subjected to left coronary artery occlusion to induce myocardial infarction, which in turn led to congestive heart failure. At 4 weeks after coronary occlusion, conivaptan (0.03, 0.1 and 0.3 mg/kg i.v.) dose-dependently increased urine volume and reduced urine osmolality in both myocardial infarction and sham-operated rats. SR121463A (0.3 mg/kg i.v.) also increased urine volume and decreased urine osmolality in myocardial infarction rats, to a degree comparable to that by conivaptan (0.3 mg/kg i.v.).

At 6 weeks after surgery, myocardial infarction rats showed increases in right ventricular systolic pressure, right atrial pressure, left ventricular end-diastolic pressure and relative weights of the heart and the lungs, and a decrease in first derivative of left ventricular pressure (dP/dt_{max})/left ventricular pressure, showing that congestive heart failure was well established. Conivaptan (0.3 mg/kg i.v.) significantly reduced right ventricular systolic pressure, left ventricular end-diastolic pressure, lung/body weight and right atrial pressure in myocardial infarction rats. Moreover, conivaptan (0.3 mg/kg i.v.) significantly increased dP/dt_{max}/left ventricular pressure. SR121463A at a dose of 0.3 mg/kg i.v. significantly decreased left ventricular end-diastolic pressure and right atrial pressure, and tended to decrease right ventricular systolic pressure and relative lung weight in myocardial infarction rats. Although the aquaretic and preload-reducing effects of SR121463A were similar to those of conivaptan, SR121463A failed to improve dP/dt_{max}/left ventricular pressure. These results suggest that dual vasopressin V_{1A} and V_2 receptor antagonists provide greater benefit than selective vasopressin V_2 receptor antagonists in the treatment of congestive heart failure.

Keywords: Conivaptan hydrochloride; Myocardial infarction; Vasopressin; Vasopressin V_{1A} receptor; Vasopressin V_2 receptor; Aquaretic effect; Hemodynamics

1. Introduction

Congestive heart failure is a syndrome which represents the end-stage in the progression of cardiac hypertrophy caused by hypertension or valvular heart disease, or the progression of ischemic heart diseases such as angina pectoris and myocardial infarction. Although angiotensin-converting enzyme inhibitors and β-adrenoceptor antagonists have been shown to improve mortality in congestive heart failure patients in recent large trials (CIBIS-II Investigators and Committees, 1999; Hjalmarson et al., 2000; Pfeffer et al., 1992; Packer et al., 2002), current drug therapy is hardly optimal. As congestive heart failure remains a fatal disease, the development of agents effective against this condition is urgently needed.

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0014-2999/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2004.11.022

In cardiac dysfunction, various neurohormonal mechanisms such as the renin–angiotensin system, sympathetic nervous system and vasopressin system are activated to maintain cardiac output following sodium and water retention in kidney, and to maintain blood supply to vital organs by peripheral vasoconstriction. The long-term result of these compensatory mechanisms, however, is to burden the diseased heart with an excessive workload, thereby leading to its eventual collapse.

Vasopressin receptors are classified into three subtypes, namely vasopressin V_{1A} receptors distributed in vascular smooth muscle and liver, vasopressin V_{1B} receptors in the anterior pituitary, and vasopressin V_2 receptors in the distal renal tubule (Birnbaumer et al., 1992; Sugimoto et al., 1994; Thibonnier et al., 1994). Given suggestions that the cardiovascular effects of vasopressin via vasopressin V_{1A} and V_2 receptors are closely implicated in a variety of cardiovascular diseases, including heart failure, hypertension, hyponatremia, renal diseases, and syndrome of inappropriate secretion of antidiuretic hormone, it is thought that vasopressin receptor antagonists will prove useful in the management of these conditions (Fujisawa et al., 1993; Naitoh et al., 1994; Laszlo et al., 1991). The development of nonpeptide, orally active vasopressin receptor antagonists which are selective for either vasopressin V_{1A} or V_2 receptors (Yamamura et al., 1991, 1992) has allowed evaluation of the pathophysiological role of vasopressin in these cardiovascular diseases.

Nonpeptide selective vasopressin V_2 receptor antagonists, however, developed owing to their aquaretic effects for possible therapeutic use in heart failure or hyponatremia (Gheorghiade et al., 2003; Shimizu, 1995) still produce a reflex increase in plasma vasopressin levels (Nishikimi et al., 1996; Laszlo et al., 1999; Ohnishi et al., 1995; Risvanis et al., 1999), and in clinical use may consequently stimulate undesired vasopressin V_{1A} receptor-derived effects, including vasoconstriction and platelet aggregation (Goldsmith, 2002; Palm et al., 2001). As a practical matter, it has been shown that vasopressin infusion produces adverse hemodynamic effects in patients with congestive heart failure, whereas vasopressin V_{1A} receptor antagonism produces hemodynamic benefits (Creager et al., 1986; Goldsmith et al., 1986).

We have discovered a novel nonpeptide vasopressin receptor antagonist, conivaptan hydrochloride, which has high affinity for rat and human vasopressin V_{1A} and V_2 receptors and rather weak affinity for oxytocin receptors (Tahara et al., 1997). We previously showed that administration of exogenous vasopressin in anesthetized dogs induces a pattern of cardiovascular dysfunction which resembles congestive heart failure in patients, and that conivaptan fully ameliorates this dysfunction (Yatsu et al., 2002). However, it remains unknown whether dual vasopressin V_{1A}/V_2 receptor antagonism is preferable to vasopressin V_2 receptor antagonism alone in congestive heart failure models.

In the present study, we investigated the effect of intravenous administration of conivaptan in rats with myocardial infarction-induced heart failure. Results were compared with those of the selective vasopressin V_2 receptor antagonist SR121463A, which has comparable affinities for rat and human vasopressin V_2 receptors as conivaptan (Serradeil-Le et al., 1996).

2. Materials and methods

2.1. Drugs

Conivaptan hydrochloride and SR121463A were synthesized at Yamanouchi Pharmaceutical Co., Ltd. (Ibaraki, Japan). The compounds were weighed, mixed with 10% w/v ethanol (special grade; Kanto Kagaku, Tokyo, Japan), stirred, then combined with 30% w/v propylene glycol (Kanto Kagaku). After dissolution by thorough stirring, the pH of the solutions was adjusted to approximately 3.3 with an appropriate volume of lactic acid (Wako Pure Chemical Industries, Ltd., Osaka, Japan), and the resulting solutions were used as conivaptan (0.3 mg/kg) and SR121463A (0.3 mg/kg) dosing formulations. Volumes were adjusted by dilution with vehicle composed of 10% ethanol, 30% propylene glycol and 60% distilled water for injection. Sham and control groups were administered the same volume of vehicle.

2.2. Preparation of heart failure rats

Post-myocardial infarction heart failure was induced in rats by ligation of the left coronary artery (Burrell et al., 1996). Briefly, male Sprague–Dawley rats aged 6 weeks underwent left thoracotomy under ether anesthesia. The incised area was extended using forceps and the pericardium was opened. The heart was then pushed out of the chest and the left anterior descending coronary artery was ligated using silk thread. The heart was immediately returned to its anatomical position and the chest was closed while slight pressure was applied from outside so that air did not remain in the chest. The skin was then sutured using wound clips. The sham-operated rats underwent the same surgical operation without actual coronary ligation. At 5 to 9 days after the operation, an electrocardiogram was recorded from the surviving ligated rats, and the presence of myocardial infarction and the size of the infarct were estimated from the appearance of abnormal Q waves. In the present study, mortality within 1 week of the operation was approximately 60%.

2.3. Measurement of aquaretic activity

At 4 weeks after the operation, 39 myocardial infarction rats survived. Thirty were randomly selected without bias and divided into five groups such that the distribution of infarct size and body weight among groups were similar, and given vehicle, conivaptan (0.03, 0.1 and 0.3 mg/kg) or

SR121463A (0.3 mg/kg) by intravenous administration. Sham rats were also divided into four groups and given vehicle or conivaptan (0.03, 0.1 and 0.3 mg/kg) by intravenous administration. Rats were then placed individually in metabolic cages and urine was collected for 3 h. Urine osmolality was measured by the freezing point depression method using an osmometer (Model 3C2, Advanced Instruments).

2.4. Measurement of hemodynamics and heart weight

At 6 weeks after the operation, the 39 surviving myocardial infarction rats were divided into four groups such that infarct size and body weight among groups were equally distributed, and given vehicle, conivaptan (0.1 and 0.3 mg/kg) or SR121463A (0.3 mg/kg) by intravenous administration. At 3 h after dosing, hemodynamic parameters were measured under pentobarbital anesthesia as follows.

A cannula was inserted into the left carotid artery and systolic and diastolic blood pressures were measured with a pressure transducer (AP-200T; Nihon Kohden, Tokyo, Japan) via the cannula. Mean blood pressure was then calculated. Heart rate was measured with a tachometer (AP-600G; Nihon Kohden) triggered by the arterial pulse wave. Left ventricular systolic pressure and left ventricular end-diastolic pressure were determined via a 2Fr Micro-tip® catheter transducer (Millar Instruments, TX, USA) inserted into the left ventricle through the right carotid artery. Peak positive first derivative of left ventricular pressure (dP/dt_{max}) was obtained with an electrodifferentiator (EQ-600G; Nihon Kohden) and dP/dt_{max}/left ventricular pressure was calculated by the division of dP/dt_{max} by left ventricular systolic pressure. Right atrial pressure and right ventricular systolic pressure were measured through a cannula placed in the right atrium and right ventricle via the right jugular vein.

After the measurement of hemodynamic parameters, the rats were sacrificed and the heart and lungs were removed. Scar tissue and remaining left ventricle including septum were dissected from the heart, and scar tissue weight divided by left ventricle including septum was calculated as a measure of infarction size. Relative weight of the heart was calculated as a measure of cardiac hypertrophy by dividing the total heart weight including scar tissue by body weight. Relative weights of the lungs were also calculated as a measure of pulmonary congestion.

2.5. Statistical analysis

Data were analyzed using SAS software (SAS Institute NC, USA) and expressed as the mean±S.E.M. In diuretic studies, results for sham-operated and myocardial infarction rats treated at each dose of conivaptan and for myocardial infarction rats treated with conivaptan or SR121463A at 0.3 mg/kg i.v. were compared using the unpaired Student's *t*-test.

In hemodynamic studies and heart weight studies, statistical analysis between the sham and myocardial infarction-control groups, the myocardial infarction-control and SR121463A groups, and the conivaptan (0.3 mg/kg i.v.) and SR121463A groups was performed using the unpaired Student's *t*-test. Those for the myocardial infarction-control group and conivaptan groups (0.1 and 0.3 mg/kg i.v.) were compared using Dunnett's multiple range test. A P value less than 0.05 was considered significant.

2.6. Ethical considerations

The protocol for this study was approved by the Animal Ethical Committee of Yamanouchi Pharmaceutical Co., Ltd.

3. Results

3.1. Aquaretic activity

Fig. 1 shows the effect of conivaptan on urine volume and urine osmolality in myocardial infarction and sham-

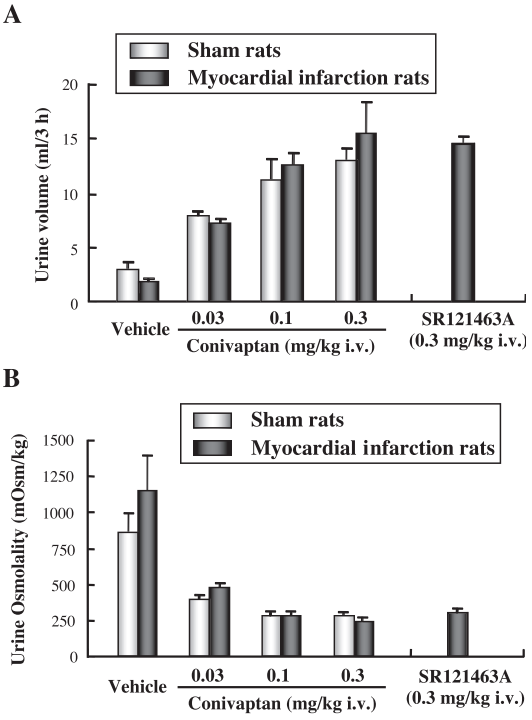

Fig. 1. Effects of conivaptan and SR121463A on urine volume (A) and osmolality (B) in rats with myocardial infarction-induced congestive heart failure (myocardial infarction rats). Columns represent the mean±S.E.M. of six experiments. Vehicle or conivaptan at 0.03, 0.1 and 0.3 mg/kg i.v. was administered to sham (open column) and myocardial infarction rats (closed column). SR121463A (0.3 mg/kg i.v.) was administered in myocardial infarction rats (closed column). No significant differences in urine volume or osmolality were observed between sham and myocardial infarction rats at each dose of conivaptan (Student's *t*-test).

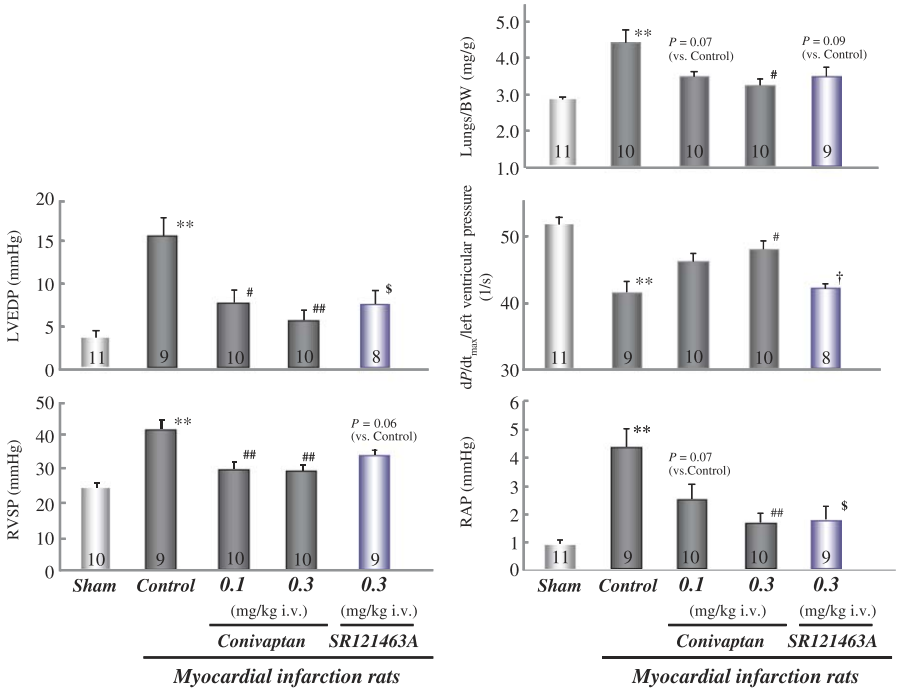

Fig. 2. Effects of intravenously administered conivaptan and SR121463A on lung weight and hemodynamic parameters in rats with myocardial infarction-induced congestive heart failure (myocardial infarction rats). Each column represents the mean±S.E.M. of 8–11 experiments. Conivaptan (0.1 and 0.3 mg/kg i.v.) and SR121463A (0.3 mg/kg i.v.) were administered to assess their effects on cardiovascular parameters in myocardial infarction rats. Statistical analysis between the sham and control groups, the control and SR121463A groups, and the conivaptan (0.3 mg/kg i.v.) and the SR121463A groups was performed with Student's *t*-test (**$P<0.01$ or $^{\$}P<0.05$ or $^{\dagger}P<0.05$, respectively). Statistical analysis between the control and conivaptan groups was performed with Dunnett's multiple comparison test ($^{\#}P<0.05$, $^{\#\#}P<0.01$). LVEDP, left ventricular end-diastolic pressure; dP/dt_{max}/left ventricular pressure; first derivative of left ventricular pressure divided by left ventricular systolic pressure; RVSP, right ventricular systolic pressure; RAP, right atrial pressure; BW, body weight.

operated rats at 4 weeks after coronary ligation. Conivaptan (0.03, 0.1 and 0.3 mg/kg i.v.) increased urine volume and reduced urine osmolality in a dose-dependent manner in both myocardial infarction and sham-operated rats, and no significant differences in aquaretic effect were observed between the two groups. Further, the aquaretic effect of conivaptan (0.3 mg/kg i.v., urine volume 15.4±3.0 ml, urine osmolality 240±33 mOsm/kg H_2O) was comparable to that of SR121463A (0.3 mg/kg i.v., urine volume 14.5±0.8 ml, urine osmolality 297±32 mOsm/kg H_2O, Fig. 1).

3.2. Changes in hemodynamics

At 6 weeks after the operation, the cardiac preload parameters such as right ventricular systolic pressure, right atrial pressure and left ventricular end-diastolic pressure were significantly elevated in myocardial infarction rats treated with vehicle (myocardial infarction-control) compared with sham rats (right ventricular systolic pressure, 24.3±1.7 mm Hg in sham vs. 41.3±3.3 mm Hg in myocardial infarction-control; right atrial pressure, 0.8±0.2 mm Hg in sham vs. 4.2±0.7 mm Hg in myocardial infarction-control; and left ventricular end-diastolic pressure, 3.6±0.9 mm Hg in sham vs. 15.2±2.7 mm Hg in myocardial infarction-control). Furthermore, dP/dt_{max}/left ventricular pressure, which shows cardiac contractility, was significantly decreased in myocardial infarction-control (41.5±2.6 s^{-1}) compared with sham rats (51.2±1.1 s^{-1}) (Fig. 2).

Intravenous bolus administration of conivaptan (0.1 and 0.3 mg/kg) significantly decreased right ventricular systolic pressure and left ventricular end-diastolic pressure in myocardial infarction rats, and at 0.3 mg/kg i.v. significantly decreased right atrial pressure. Moreover, conivaptan (0.3 mg/kg i.v.) significantly increased dP/dt_{max}/left ventricular

Table 1
Effects of conivaptan and SR121463A on hemodynamics in myocardial infarction rats at 6 weeks after coronary ligation

Group	MBP (mm Hg)	HR (beats/min)	LVSP (mm Hg)
Sham	117±4 (11)	370±9 (11)	162±6 (11)
MI-control	101±7[a] (10)	389±8 (10)	132±6[b] (9)
MI-conivaptan (0.1 mg/kg i.v.)	110±6 (10)	384±9 (10)	133±6 (10)
MI-conivaptan (0.3 mg/kg i.v.)	103±4 (10)	383±8 (10)	128±4 (10)
MI-SR121463A (0.3 mg/kg i.v.)	95±6 (9)	395±10 (9)	117±10 (8)

Values are mean±S.E.M. Numbers in parentheses represent the number of experiments. MI, myocardial infarction; MBP, mean blood pressure; HR, heart rate; LVSP, left ventricular systolic pressure.

[a] $P<0.05$ vs. sham group (Student's *t*-test).

[b] $P<0.01$ vs. sham group (Student's *t*-test).

Table 2
Effects of conivaptan and SR121463A on heart weights in myocardial infarction rats at 6 weeks after coronary ligation

Group (n)	Scar/LV+septum (mg/mg)	Body weight (g)	Heart/body weight (mg/g)	LV/body weight (mg/g)	RV/body weight (mg/g)
Sham (11)	N.D.	479±7	2.49±0.04	1.77±0.03	0.50±0.02
MI-control (10)	0.153±0.018	464±10	3.12±0.09[a]	1.75±0.05	0.71±0.04[a]
MI-conivaptan (0.1 mg/kg i.v.) (10)	0.154±0.016	462±16	2.95±0.07	1.69±0.05	0.65±0.04
MI-conivaptan (0.3 mg/kg i.v.) (10)	0.154±0.017	465±12	2.94±0.07	1.72±0.05	0.61±0.02
MI-SR121463A (0.3 mg/kg i.v.) (9)	0.155±0.016	467±13	3.01±0.10	1.73±0.05	0.66±0.04

Values are mean±S.E.M. Numbers in parentheses represent the number of experiments. N.D., not detected. MI, myocardial infarction rats; LV, left ventricle; RV, right ventricle.
[a] $P<0.01$ vs. sham group (Student's t-test).

pressure in these rats (Fig. 2). In contrast, no significant changes were seen in heart rate or mean blood pressure between the conivaptan-treated and control myocardial infarction rats (Table 1). SR121463A (0.3 mg/kg i.v.) also significantly decreased right atrial pressure and left ventricular end-diastolic pressure, and tended to decrease right ventricular systolic pressure in myocardial infarction rats. Unlike conivaptan, SR121463A failed to increase dP/dt_{max}/left ventricular pressure in myocardial infarction rats, which was significantly low compared with values with conivaptan (0.3 mg/kg i.v.).

3.3. Infarct size and tissue weight

There was no difference in infarct size among the myocardial infarction-experimental groups and no infarction was found in the sham rats (Table 2). With respect to organ weight, relative weights of the heart and relative weights of the lungs were significantly increased in myocardial infarction-control rats at 6 weeks after ligation (Table 2 and Fig. 2). Intravenous administration of conivaptan (0.3 mg/kg) and SR121463A (0.3 mg/kg) decreased relative weights of the lungs, but had no effect on relative weights of the heart.

4. Discussion

Myocardial infarction induced by coronary ligation in rats is a widely used experimental model of congestive heart failure. It is characterized by the impairment of left ventricular function, development of cardiac remodeling and activation of neurohumoral factors. These characteristics show a reasonable resemblance to those of congestive heart failure in patients, and the effects of drugs in this model are therefore considered an important reference in estimating their effects in patients with post-infarct congestive heart failure.

Impairment of cardiac function results in the activation of several neurohormonal systems, including the renin–angiotensin system, sympathetic nervous system and endothelin or vasopressin system. These compensatory mechanisms both maintain cardiac output by enhancing cardiac contractility and increasing circulatory fluid volume via the promotion of sodium and water retention, and assist the maintenance of blood flow to vital organs by peripheral vasoconstriction.

Elevated plasma vasopressin levels due to inappropriate secretion have been identified in patients with congestive heart failure. Vasopressin secreted into the circulatory system exerts diverse effects in the periphery. Among vasopressin V_{1A} receptor-mediated effects, vasopressin raises peripheral vascular resistance, with a resultant increase in cardiac afterload, induces coronary vasoconstriction (Fernandez et al., 1998; Walker et al., 1988) together, leading to myocardial ischemia followed by cardiac depression. In this regard, it was reported that intravenous vasopressin infusion suppressed left ventricular contractility in normal dogs (Yatsu et al., 2002). Moreover, vasopressin V_2 receptor-induced water retention in the kidney collecting ducts augments cardiac preload as a consequence of an increase in circulatory fluid volume. These concomitant effects work to depress the already impaired cardiac function, and vasopressin is considered to be an aggravating factor in congestive heart failure.

Conivaptan is a novel nonpeptide vasopressin receptor antagonist that shows high affinity for both vasopressin V_{1A} and V_2 receptors. In previous in vivo studies, intravenous administration of conivaptan inhibited exogenous vasopressin-induced pressor responses in pithed rats, and increased urine volume without increasing urinary electrolytes in dehydrated conscious rats and dogs (Tahara et al., 1997; Yatsu et al., 1997).

In the present study, conivaptan (0.03 to 0.3 mg/kg i.v.) dose-dependently increased urine volume and simultaneously decreased urine osmolality below the plasma osmolality of 300 mOsm/kg H_2O, a characteristic of aquaretics, in myocardial infarction rats. This finding is consistent with previous reports that conivaptan (Wada et al., 2002) and a vasopressin V_2 receptor antagonist (Burrell et al., 1998) elicited nearly equal aquaretic effects in sham and myocardial infarction rats 4 weeks after ligation with impaired cardiac function and ventricular remodeling. In patients with congestive heart failure, Szatalowicz et al. (1981) reported inappropriately high plasma vasopressin levels in spite of the presence of hypoosmolality which should have suppressed plasma vasopressin levels. Further, Goldsmith et al. (1986) found that plasma vasopressin levels in decompen-

sated congestive heart failure patients could not be suppressed by acute water loading. These findings show that vasopressin secretion in patients with heart failure is inappropriately stimulated and may result in the complication of dilutional hyponatremia. Given that water retention-induced hyponatremia is a major predictor of mortality in patients with congestive heart failure, the aquaretic effect of conivaptan is considered to be beneficial, and to represent an alternative approach to the relief of symptoms and the amelioration of the severity of heart failure.

With respect to hemodynamics in myocardial infarction rats at 6 weeks after coronary ligation, elevations in right ventricular systolic pressure and left ventricular end-diastolic pressure, which are cardiac preload parameters; a decrease in dP/dt_{max}/left ventricular pressure, an indicator of cardiac contractility; and increases in right atrial pressure and relative weights of the lungs, which are markers of systemic and pulmonary congestion were observed. In addition, an increase in corrected heart weight showed the presence of cardiac remodeling. These changes clearly show that congestive heart failure was well established in myocardial infarction rats at 6 weeks after surgery.

Conivaptan was shown to significantly reduce the left ventricular end-diastolic pressure, right atrial pressure and lung/body weight in the myocardial infarction rats. Given that conivaptan exerted an aquaretic effect, the decrease in cardiac preload and pulmonary congestion observed in this study must be attributed to an increase in water excretion mediated by vasopressin V_2 receptor antagonism. We consider it promising that SR121463A, a vasopressin V_2 receptor antagonist, showed a closely similar effect to conivaptan on these preload parameters.

In the present study, however, conivaptan and SR121463A differed in their effect on cardiac contractility in myocardial infarction rats, with conivaptan significantly increasing dP/dt_{max}/left ventricular pressure and SR121463A having no effect. In previous studies in an experimental model and in patients whose plasma vasopressin levels were elevated, a peptide vasopressin receptor antagonist that shows selectivity for vasopressin V_{1A} receptors was reported to significantly improve hemodynamics with reduced peripheral vascular resistance (Nicod et al., 1986; Raya et al., 1990; Creager et al., 1986). In addition, vasopressin is known to produce potent coronary vasoconstriction via vasopressin V_{1A} receptors, which results in myocardial ischemia (Boyle and Segel, 1986; Wilson et al., 1980). Conivaptan has been shown to improve cardiac contractility in pacing-induced heart failure in dogs before any diuretic effect was exerted (Yatsu et al., 1999). Taken together, these findings suggest that vasopressin V_{1A} receptor antagonism has the potential to directly reduce cardiac afterload and suppress coronary constriction, resulting in an improvement in cardiac contractility in congestive heart failure.

Acute water depletion induced by the aquaretic effect via vasopressin V_2 receptor blockade stimulates vasopressin secretion from the hypothalamo-neurohypophysial system, and it is reported that vasopressin V_2 receptor antagonism in rats and dogs with congestive heart failure reflexively increases plasma vasopressin levels (Nishikimi et al., 1996; Naitoh et al., 1994). Therefore, after vasopressin V_2 receptor blockade, the possibility exists that plasma vasopressin concentration may rise high enough to stimulate undesired vasopressin V_{1A} receptor-derived effects. Given that conivaptan demonstrates potent vasopressin V_{1A} receptor antagonistic activity as well as vasopressin V_2 receptor antagonistic activity, it could inhibit vasopressin V_{1A} receptor-mediated cardiac depression by excessive release of vasopressin, leading to improvement in cardiac contractility. In contrast, the selective vasopressin V_2 receptor antagonist SR121463A would be unable to completely block all of the vasopressin V_{1A} receptor-mediated cardiovascular effect. Although the results of the present study suggest that dual vasopressin V_{1A}/V_2 receptor antagonists like conivaptan provide greater benefits than vasopressin V_2 receptor-selective antagonists in the treatment of patients with depressed cardiac function due to their obviation of any compensatory counteraction of vasopressin, we obtain no direct evidence that vasopressin excessively released by counteraction of the aquaretic effect has a significant role on cardiac function. Further investigation is needed to clarify this point.

In summary, the present study demonstrated that the dual vasopressin V_{1A}/V_2 receptor antagonist conivaptan exerted an aquaretic effect and decreased cardiac preload in myocardial infarction rats. Moreover, conivaptan improved left ventricular contractility in myocardial infarction rats, in contrast to the vasopressin V_2 receptor selective antagonist SR121463A, which failed to do so. These results suggest that the dual vasopressin V_{1A} and V_2 receptor antagonist conivaptan will be more beneficial in the treatment of congestive heart failure than vasopressin V_2 receptor-selective antagonists.

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