Tolvaptan for Heart Failure Patients with Volume Overload

Masatsugu Hori

Published online: 3 May 2011
© Springer Science+Business Media, LLC 2011

Introduction

Edema is defined as a state of extracellular fluid accumulation, mostly of intercellular fluid, and clinically as a state where the subcutaneous tissues become enlarged because of the accumulation of interstitial fluid. Edema is often observed in daily clinical practice and the most serious causes include heart failure (HF), hepatic cirrhosis, and nephrotic syndrome.

Patients with HF are often in a volume overload state because of the increases in extracellular volume, plasma volume, and blood volume; collectively, these disorders result in lower limb edema, jugular venous distension, hepatomegaly, and pulmonary congestion. In patients with HF, volume overload usually accounts for an increase in body weight of as much as 2–5 kg [1]. Volume overload in patients with heart diseases is generally called “cardiac edema”.

Pathogenesis of volume overload in HF

Heart failure, a major cause of volume overload, is a syndrome that impairs the pumping function of the heart due to myocardial disorders, which leads to an absolute deficiency or relatively insufficient blood flow to meet the oxygen requirements of the peripheral organs [1]. In response to cardiac dysfunction, compensatory mechanisms are activated to increase the cardiac output, which entail

retention of body fluid and increasing the circulatory blood volume to maintain blood pressure. If the compensatory mechanisms work appropriately, no symptoms will emerge; however, if cardiac function deteriorates further, despite the compensatory mechanisms, extracellular volume expansion may occur and venous pressure increases. In turn, this increases the capillary pressure, causing leakage of intracapillary fluid out of the capillaries, resulting in overt edema.

Decreased plasma osmotic pressure is another factor which is involved in volume overload. The plasma osmotic pressure represents the osmolality of plasma proteins and is essential for intravascular fluid maintenance. As the plasma protein volume decreases, the plasma osmotic pressure declines, causing leakage of intravascular fluid out of the blood vessels. Patients with chronic HF often suffer from nutritional disorders and/or gastrointestinal malabsorption, which may promote hypoproteinemia causing a decrease in plasma osmotic pressure.

The volume overload in HF patients is ultimately caused by insufficient renal excretion of fluid and sodium (Na^+). Recent studies have demonstrated the involvement of neurohormonal factors in renal excretion of water and electrolytes in HF patients. In particular, the sympathetic nervous system and the renin–angiotensin–aldosterone system, as well as vasopressin, are critical mediators of volume overload in HF [2]. Circulatory dysfunction may reduce baroreceptor loading in the left ventricle, carotid sinus and aortic arch, which generates afferent signals to the cardiac regulatory center in the brain. This activates the supraoptic nuclei and paraventricular nuclei of the hypothalamus, causing the release of vasopressin from the posterior lobe of the pituitary. In parallel with this pathway, the afferent signals activate the sympathetic nervous system and enhance the renal sympathetic nerve activity.

M. Hori (✉)
Osaka Medical Center for Cancer and Cardiovascular Diseases,
1-3-3 Nakamichi, Higashinari-ku,
Osaka 537-8511, Japan
e-mail: hori-ma@mc.pref.osaka.jp

This stimulates the release of renin and angiotensin I, thus activating the renin–angiotensin–aldosterone system. Angiotensin II promotes the reabsorption of Na^+ in the renal tubules, despite a reduction in the glomerular filtration rate and/or renal blood flow, and also enhances reabsorption of Na^+ in the renal collecting tubules via aldosterone secretion. Accordingly, aberrant activation of neurohormones causes a marked volume overload in HF patients.

The role of vasopressin in the volume overload in HF

Vasopressin, also known as arginine vasopressin (AVP) and antidiuretic hormone, is involved in the volume overload in patients with chronic HF. Vasopressin is a neuropeptide hormone produced in supraoptic nuclei and paraventricular nuclei of the hypothalamus, and is released into the blood from the posterior lobe of the pituitary where the axon arising from the nerve cell body terminates. Vasopressin secretion from neuronal cells in the hypothalamus is controlled by baroreceptors and osmoreceptors, and is also influenced by abnormalities in the central nervous system, infections, cardiopulmonary disorders, and endocrine disorders as well as various medications. The blood vasopressin concentration significantly increases in response to a decrease in blood pressure or an increase in serum osmolality. Vasopressin acts via V_{1a} receptors to constrict blood vessels and via the V_2 receptor in the kidney to enhance water reabsorption [3]. These receptors are both transmembrane G protein-coupled receptors, and the V_2 receptors mediate the antidiuretic effects of vasopressin causing volume overload.

HF patients are at a high risk of developing volume overload or inappropriate fluid excretion because of enhanced vasopressin secretion. Such patients often exhibit electrolyte imbalances, particularly hyponatremia of undetermined etiology. In patients with hyponatremia, the use of conventional diuretics to treat volume overload may worsen the electrolyte abnormalities with excessive excretion of electrolytes and aggravation of hyponatremia, which may cause nervous system and cardiovascular complications [4, 5]. Hyponatremia induced by diuretics may result in stupor, coma or even death, while hypokalemia may cause fatal arrhythmia.

Standard therapies for the volume overload in HF

The fundamental therapy for volume overload in HF is a water- and salt-restricted diet to prevent fluid and/or Na^+ volume overload. However, remission is not achieved in many cases despite a water- and salt-restricted diet,

prompting the use of diuretics. Diuretics are the most effective class of medication to relieve the symptoms such as jugular venous distension, hepatomegaly, lower limb edema and pulmonary congestion. The Japanese Circulation Society Guidelines for the Diagnosis and Treatment of Chronic Heart Failure (revised in 2005) [1] classifies diuretic therapies into Class I recommended therapy for the treatment of symptoms associated with volume overload in patients with chronic HF. Diuretic therapy can decrease venous return and lower the preload. In turn, the decreased preload lowers the left ventricular filling pressure, and improves congestion.

Loop diuretics, thiazide diuretics and anti-aldosterone drugs are the most commonly used to treat volume overload in patients with HF. Loop diuretics are the most potent of these diuretics and are currently the first-line medication for volume overload in patients with HF. The Guidelines for the Diagnosis and Treatment of Chronic Heart Failure recommends starting with a low dose, equivalent to 10–20 mg/day of furosemide, and dose titrating according to the symptoms [1]. Thiazide diuretics are strong antihypertensive drugs with a relatively mild diuretic effect and are thus often used in patients with hypertension or with modest edema. Since thiazide diuretics have additive effects when used in combination with loop diuretics, the concomitant use of both drugs should be considered for patients with inadequate effects by a loop diuretic monotherapy. Anti-aldosterone drugs possess a weak diuretic effect but prevent the loss of potassium or magnesium, and should be considered for patients in whom serum electrolyte depletion is a major concern. The RALES study [6] showed that treatment with low-dose anti-aldosterone drug (spironolactone) without much diuretic effect could also reduce all-cause mortality and readmission rates in severe HF patients (NYHA class IV). The EMPHASIS-HF study [7] also showed that treatment with eplerenone could also reduce all-cause mortality and readmission rates in patients with systolic heart failure and mild symptoms (NYHA class II); thus, anti-aldosterone drugs provide a useful therapy for HF.

Loop diuretics and thiazide diuretics are collectively known as saluretic drugs because they may cause serum electrolyte depletions, i.e., hyponatremia and hypokalemia. A decrease in serum Na^+ concentration often leads to headache, vomiting, muscle spasm, lethargy and disorientation. Seizures, coma, psychiatric disorders, respiratory arrest and brain stem herniation may also occur in severe and acute cases [8]. On the other hand, a decrease in serum potassium concentration may lead to fatal arrhythmia in HF patients. In addition, the concomitant use of digitalis often leads to digitalis intoxication. Hypokalemia also impairs glucose tolerance or worsens pre-existing impaired glucose tolerance. Since saluretic drugs exert an antihypertensive

effect, dizziness and/or a light-headed feeling associated with hypotension may be observed. Such symptoms contraindicate an increase in the dose of loop diuretics or the addition of thiazide diuretics. This may also indicate that a sufficient diuretic effect cannot be achieved in some patients. Thus, a novel diuretic that does not enhance electrolyte excretion is required for these HF patients.

Even without any concern of adverse drug reactions, such as electrolyte depletion or hypotension, the effects of conventional diuretics can be attenuated because of decreased cardiac output and/or impaired renal function. In fact, the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME CHF) [9] showed that many patients who had been hospitalized for decompensated HF were discharged from hospital even with residual congestion. In this study, the combined rate of mortality and readmission at 60 days after discharge was reported to be as much as 35% [9]. This is mainly because electrolyte imbalance, hypotension and prerenal azotemia. Activation of the renin–angiotensin–aldosterone system is often related to the use of diuretics, and therapies to optimize the excretion of excess fluid are often limited. Accordingly, a novel diuretic that possesses a different mechanism of action and exerts combined effects with other diuretics may be useful for these HF patients.

Despite the importance of the clinical development of new therapies for decompensated HF, very few treatments have been introduced in the last 10 years. For volume overload in HF patients, a novel diuretic with a new mechanism of action has long been needed; it is expected to have additive effects when combined with the conventional diuretics, without an increase in electrolyte excretion. Selective antagonists of vasopressin V_2 receptors, which promote excretion of free water without causing electrolyte imbalances, are likely to be clinically useful for treatment of diseases associated with hyponatremia or fluid overload with hyponatremia. Drugs with these properties are called “aquaretics”.

Tolvaptan (Fig. 1) is a nonpeptide V_2 receptor antagonist that selectively and competitively inhibits vasopressin binding to the V_2 receptors. Tolvaptan is an aquaretic that promotes the excretion of excess fluid without increasing electrolyte excretion. Since the mechanism of action of tolvaptan differs from that of conventional diuretics, additional diuretic effects are expected in patients with volume overload when administered in combination with other diuretics. In particular, for patients in whom an increase in the dosage of conventional diuretics is contraindicated because of electrolyte depletion or associated adverse effects, tolvaptan is expected to exert further diuresis without an increase in electrolyte excretion through selective inhibition of water reabsorption in the kidney.

Fig. 1 Structural formula of tolvaptan. *N*-{4-[(5*RS*)-7-Chloro-5-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl]-3-methylphenyl}-2-methylbenzamide

Thus, tolvaptan could offer an alternative option for the treatment of edema and volume overload. Indeed, tolvaptan was approved for treatment of hyponatremia with or without volume overload in the US and for the treatment of Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in Europe in 2009.

Purpose of the supplement: therapeutic targets and clinical significance of tolvaptan

The purpose of this supplement is to collate the results of clinical and nonclinical studies for the selective, nonpeptide V_2 receptor antagonist tolvaptan, and to provide information necessary for the use of tolvaptan. This supplement covers five clinical studies [10–14], including a Japanese phase 1 study [13], and four nonclinical studies (2 pharmacological studies [15, 16], a pharmacokinetic study [17], and a safety pharmacology/toxicity study [18]) as shown in the Table of Contents.

A double-blind, placebo-controlled study of tolvaptan (the QUEST study) reported in this supplement [12] enrolled HF patients with uncontrollable volume overload despite the use of conventional diuretics. These eligible patients were treated with 15 mg tolvaptan, once-daily for 7 days, as an add-on to their conventional diuretic therapies. Tolvaptan increased urine volume, with an additive effect to the conventional diuretics. Furthermore, tolvaptan significantly decreased body weight and improved the symptoms of volume overload, including jugular venous distension, hepatomegaly, and lower limb edema in HF patients. Tolvaptan (15 mg/day) together with the conventional diuretics included higher than normal doses of furosemide (100–400 mg/day) elicited potent water diuresis, regardless of the type and dose of the concomitant diuretics. Thus, tolvaptan can improve the volume overload by rescuing the insufficient effects of conventional diuretics. In particular, tolvaptan could be useful in elderly patients who are at higher risk of electrolyte depletion and hypotension associated with diuretics.

Clinical and nonclinical studies performed to date suggest that tolvaptan has the following properties:

- 1) Tolvaptan has no intrinsic antidiuretic effect, but has a strong antagonistic effect against V_2 receptors [19, 20].
- 2) Unlike saluretic drugs, tolvaptan has an aquaretic effect without increasing urinary electrolyte excretion [10, 14, 20, 21].
- 3) Tolvaptan maintains its aquaretic effect in combination with saluretic drugs [21].
- 4) Tolvaptan maintains its aquaretic effect during the multiple-dose period, and improves volume overload and HF symptoms in combination with saluretic drugs [11–14].
- 5) Tolvaptan does not affect neurohormonal factors, renal function, or hemodynamic parameters, such as blood pressure and heart rate [12, 14, 15, 22].
- 6) Tolvaptan does not decrease the serum Na^+ concentration and improves hyponatremia [12, 14].

Thus, tolvaptan is a promising drug for potent water excretion in the treatment of uncontrollable edema and congestion in HF.

Disclosures There are no conflicts of interest associated with this article.

References

1. Japanese Circulation Society. Guidelines for the diagnosis and treatment of cardiovascular disease (Joint Study Group Report 2004): guidelines for the diagnosis and treatment of chronic heart failure (revised 2005). http://www.j-circ.or.jp/guideline/pdf/JCS2005_matsuzaki_h.pdf. Accessed 27 Oct 2010.
2. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med*. 1999;341:577–85.
3. Goldsmith SR, Gheorghiade M. Vasopressin antagonism in heart failure. *J Am Coll Cardiol*. 2005;46:1785–91.
4. Rivera-Santos A, Star R. Sodium: volume depletion and hyponatremia. In: Seldin D, Giebisch G, editors. *Diuretic agents—clinical physiology and pharmacology*. San Diego: Academic; 1997. p. 559–69.
5. Palmer BF. Potassium disturbances associated with the use of diuretics. In: Seldin D, Giebisch G, editors. *Diuretic agents—clinical physiology and pharmacology*. San Diego: Academic; 1997. p. 571–83.
6. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709–17.
7. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11–21.
8. Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000;342:1581–9.
9. Cuffe MS, Califf RM, Adams KF, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541–7.
10. Kim SR, Hasunuma T, Sato O, et al. Pharmacokinetics, pharmacodynamics and safety of tolvaptan, a novel, oral, selective nonpeptide AVP V_2 -receptor antagonist: results of single- and multiple-dose studies in healthy Japanese male volunteers. *Cardiovasc Drugs Ther*. 2011; submitted.
11. Matsuzaki M, Hori M, Izumi T, et al. Effects of tolvaptan on volume overload in Japanese patients with heart failure: Results of a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Cardiovasc Drugs Ther*. 2011; submitted.
12. Matsuzaki M, Hori M, Izumi T, et al. Efficacy and safety of tolvaptan in heart failure patients with volume overload despite the standard treatment with conventional diuretics: a phase III, randomized, double-blind, placebo-controlled study (QUEST Study). *Cardiovasc Drugs Ther*. 2011; submitted.
13. Fukunami M, Matsuzaki M, Hori M, et al. Efficacy and safety of tolvaptan in heart failure patients with sustained volume overload despite the use of conventional diuretics: a phase III open-label study. *Cardiovasc Drugs Ther*. 2011; submitted.
14. Inomata T, Izumi T, Matsuzaki M, et al. Phase III clinical pharmacology study of tolvaptan. *Cardiovasc Drugs Ther*. 2011; submitted.
15. Onogawa T, Sakamoto Y, Nakamura S, et al. Effects of tolvaptan on systemic and renal hemodynamic function in dogs with congestive heart failure. *Cardiovasc Drugs Ther*. 2011; submitted.
16. Miyazaki T, Sakamoto Y, Yamashita T, et al. Anti-edematous effects of tolvaptan in experimental rodent models. *Cardiovasc Drugs Ther*. 2011; submitted.
17. Furukawa M, Hirota M, Okumura H, et al. Nonclinical pharmacokinetics of tolvaptan. *Cardiovasc Drugs Ther*. 2011; submitted.
18. Oi A, Ito N, Morishita K, et al. Nonclinical safety profile of tolvaptan. *Cardiovasc Drugs Ther*. 2011; submitted.
19. Yamamura Y, Nakamura S, Itoh S, et al. OPC-41061, a highly potent human vasopressin V_2 -receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. *J Pharmacol Exp Ther*. 1998;287:860–7.
20. Miyazaki T, Fujiki H, Yamamura Y, Nakamura S, Mori T. Tolvaptan, an orally active vasopressin V_2 -receptor antagonist - pharmacology and clinical trials. *Cardiovasc Drug Rev*. 2007;25:1–13.
21. Hirano T, Yamamura Y, Nakamura S, Onogawa T, Mori T. Effects of the V_2 -receptor antagonist OPC-41061 and the loop diuretic furosemide alone and in combination in rats. *J Pharmacol Exp Ther*. 2000;292:288–94.
22. Costello-Boerrigter LC, Smith WB, Boerrigter G, et al. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. *Am J Physiol Ren Physiol*. 2006;290:F273–8.