Preliminary Report of Tolvaptan Treatment in Japanese Patients With Heart Failure

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Summary

While diuretic drugs are commonly used in patients with congestive heart failure, the efficacy of their long-term use still remains controversial. Recently, a new class of diuretics, vasopressin receptor 2 antagonists, has been launched, and tolvaptan is one such drug. We describe our initial experience with this novel agent. Tolvaptan is potentially useful for treatment of heart failure patients with fluid overload who are refractory to conventional diuretic therapies. (Int Heart J 2012; 53: 72-74)

Key words: Tolvaptan, Fluid overload, Heart failure, V2 antagonist

Heart failure is a major public problem and one of the leading causes of hospitalization and morbidity in the Western world and Japan. Numerous patients are hospitalized with heart failure induced by fluid overload. In addition to the evidence-based approaches including angiotensin-converting enzyme inhibitors and beta-adrenergic blocking agents, diuretics and carperitide have been widely used in the treatment of heart failure patients in Japan. Among diuretic-related side effects, the presence of hyponatremia is independently associated with adverse outcome in heart failure patients. To address this safety issue, tolvaptan: a once-daily, orally available vasopressin receptor 2 antagonist, has recently been launched for the management of heart failure patients in Japan. Here we describe our initial experience with this novel class agent.

Case Report

Case 1: A 75-year-old man was admitted to our hospital with complaints of worsening dyspnea and leg edema. He underwent mitral valve replacement for mitral regurgitation 20 years earlier and returned for follow-up visits. Although he had been taking carvedilol, enalapril, spironolactone, and indapamide, he had been repeatedly hospitalized for worsening heart failure. On admission, his blood pressure and pulse rate were 128/58 mmHg and 86 per minute, respectively, and his body weight (BW) was 95 kg, which was an increase of approximately 10 kg from his baseline BW. The breath sound was diminished at the base of his right lung, and severe pretibial pitting edema was observed. Chest X-rays showed marked cardiomegaly and massive pleural effusion. Echocardiography demonstrated decreased left ventricular (LV) systolic function with LV dilatation (LV end-diastolic diameter 64 mm, end-systolic diameter 55 mm, and LV ejection fraction 29%). Right ventricular systolic pressure (RVSP) was estimated to be 50 mmHg and the inferior vena cava (IVC) was dilated (expiratory IVC diameter 25 mm, inspiratory 18 mm). Laboratory data showed mild renal dysfunction (estimated glomerular filtration rate: eGFR 32.5 mL/minute/m²), normal liver function, an elevated plasma brain natriuretic peptide (BNP) level (752 pg/mL), and slight lowering of the serum sodium level (134 mEq/L).

The diagnosis was acute exacerbation of congestive heart failure, and treatment with intravenous atrial natriuretic peptide (carperitide 0.05 μg/kg/minute), intravenous furosemide (40 mg/day), thoracocentesis, and biphasic positive airway pressure ventilation was started in the cardiac care unit (CCU). His body weight decreased to 77 kg. The course in the CCU was satisfactory, and about 2 weeks later he was transferred to a general ward. After we tapered off carperitide, his urine volume decreased and his heart failure worsened again (Figure 1). Therefore, we started tolvaptan to control his body fluid balance. In this case, tolvaptan was initiated with a dose of 3.75 mg/day, which was a quarter of the regular dose. Two days later, we raised the dose to 7.5 mg/day. His urine volume markedly increased and 8 days later he reached his ideal fluid balance (BW 74 kg, BNP 215 pg/mL). The effects of tolvaptan were confirmed by the decrease of urine osmolarity (Figure 1). He was in stable condition after discontinuation of tolvaptan for a week, and he was discharged from our hospital. During treatment with tolvaptan, he did not develop any complications such as hyponatremia, hypovolemia, or worsening of renal...

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This research was funded by a grant from the Japan Society for the Promotion of Science (JSPS) through the “Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program)”, initiated by the Council for Science and Technology Policy (CSTP).

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Received for publication August 22, 2011.
Revised and accepted October 13, 2011.
function. We tapered off tolvaptan over 2 days. There were no signs of worsening heart failure at the first outpatient visit.

**Case 2:** A 49-year-old man was admitted to our hospital because of worsening dyspnea on effort and leg edema that had persisted for a month. He had a history of anterior myocardial infarction, diabetes mellitus, and renal dysfunction. Despite taking carvedilol, telmisartan, imidapril, spironolactone, and furosemide, he had been frequently hospitalized for heart failure. On admission, his blood pressure and pulse rate were 160/100 mmHg and 101 per minute, respectively, and his BW was 108 kg, which was about 20 kg more than his baseline BW. The breath sounds were decreased at the base of both lungs, and pretibial pitting edema was observed. Chest X-rays showed cardiomegaly with slight bilateral pleural effusion.
Echocardiography revealed LV dilatation and LV systolic dysfunction with segmental asynergy in the anterior wall (LV end-diastolic diameter 60 mm, end-systolic diameter 50 mm, LV ejection fraction 34%). RVSP was estimated to be high (50 mmHg) and the IVC was significantly dilated (expiratory IVC diameter 30 mm, inspiratory 25 mm). Laboratory data disclosed moderate renal dysfunction (eGFR 26.8 mL/minute/1.73 m²), markedly elevated BNP (1456 pg/mL), normal liver function, and normal electrolyte levels with serum sodium of 143 mEq/L. A diagnosis of acute exacerbation of congestive heart failure was made, and treatment with intravenous administration of furosemide 10 mg/day was started in addition to his usual prescribed drugs (Figure 2). Since we could not control his fluid balance, we started to administer tolvaptan at 7.5 mg/day on hospital day 5 instead of intravenous furosemide (Figure 2). During the first 2 weeks of tolvaptan therapy, his BW decreased by 15 kg compared with that on admission, however, it did not completely relieve his symptoms. Thereafter, we raised the tolvaptan dose to 15 mg/day on day 23. His symptoms were finally relieved on day 30 (BNP 440 pg/mL), and he left the hospital with discharge medication including tolvaptan (15 mg/day). His course after discharge was stable, and there were no complications such as hypovolemia, hypernatremia, or worsening of renal function during follow-up in the outpatient clinic. After 3 weeks of tolvaptan treatment, his urine osmolality remained low (Figure 2).

Discussion

Loop diuretics, aldosterone antagonists and carperitide play a central role in the management of acute congestive heart failure in Japan. Carperitide is effective not only as a diuretic but also as a vasodilator and a renin-angiotensin system inhibitor. Since carperitide has to be infused intravenously, it needs to be replaced by other orally-administered diuretics, including loop diuretics, prior to hospital discharge. The dose of loop diuretic is, however, an independent negative predictor of outcome in heart failure patients. As observed in case 1, we had difficulty in discontinuing carperitide because his daily urine volume decreased soon after it was ceased. In such patients, tolvaptan may be helpful to withdraw this intravenous drug and shorten the hospitalization period in patients who are apparently dependent on carperitide.

Although tolvaptan markedly increased urine output for the initial few days, this effect decreased within a week (cases 1 and 2). Moreover, according to the measurement of urine osmolarity (Figure 2), sustained water diuretic effects of this agent have been confirmed even after 3 weeks of treatment as previously described. Tolvaptan is now recommended only for short-term use in Japan, although the EVEREST study has shown the safety of long-term use of this drug. According to the ACTIV in the CHF study, tolvaptan may decrease mortality in heart failure patients with severe systemic congestion, renal dysfunction, and hyponatremia. Tolvaptan seems to be beneficial in patients with hyponatremia by normalizing serum sodium levels. Both of our cases had severe congestive heart failure, and tolvaptan was strikingly effective in relieving their symptoms and attaining ideal fluid balance. However, in order to fully understand the long-term efficacy of tolvaptan, we need to closely follow the clinical courses of Japanese heart failure patients. Future investigation in Japan is necessary to define the role of tolvaptan in a variety of clinical settings and patient populations, particularly in terms of long-term safety and efficacy.