

[REVIEW ARTICLE]

Hemodynamic and Hormonal Effects of Tolvaptan for Heart Failure

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Abstract:

Tolvaptan (TLV) is a diuretic agent administered for heart failure (HF) only in Japan. Many clinical findings have been obtained from the accumulation of clinical experience, and the administration of TLV reportedly avoids causing a reduction in the renal function. In addition, TLV has been reported to exert effects other than diuresis. The early start of TLV after hospitalization shortens the length of the hospital stay, and continuous TLV after discharge extends the period until re-hospitalization of HF patients. TLV is thought to function via vasopressin V2 receptor antagonism. However, no significant differences in the long-term prognosis were noted between the group using TLV and not using TLV in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) trial, and effects other than diuresis are not useful for all HF patients. Therefore, it is necessary to identify patients who may experience effects other than diuresis with TLV administration. The accumulation of more patients and findings from further large-scale clinical trials will be necessary in order to clarify these points.

Key words: tolvaptan, vasopressin, V2 receptor

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Introduction

In Japan, tolvaptan (TLV) was approved for heart failure (HF) patients suffering from fluid retention despite receiving standard treatment with conventional diuretics in December 2010 (1). However, while TLV is used to treat such HF patients in Japan, this agent has only been used to treat hyponatremia in other countries. It is no exaggeration to say that TLV, which operates via a novel diuretics mechanism that contrasts with water diuretics, has become an indispensable agent in the clinical setting based on the accumulation of seven years of clinical research. However, some clinical points remain unclear.

In this review, we focused on the mechanisms by which TLV exerts its activity and the results of clinical trials.

The Diuretic Mechanism of Tolvaptan

Diuretics (especially loop diuretics) have a central role in the treatment of HF, and the Japanese Cardiac Registry of

Heart Failure in Cardiology (JCARE-CARD) trial in 2003 reported that loop diuretics were used in 87.0% of cases (2). The frequency of use of diuretics has declined somewhat over the years since, but the CHART-2 study in 2015 reported that loop diuretics were still used in 55.5% of cases (3). However, despite their utility, increasing the dose of loop diuretics is known to increase the mortality rate of HF (4). One reason for this is a worsening renal function (WRF) caused by loop diuretics (5).

TLV reduces the WRF not only during hospitalization but also in the medium term after discharge (6, 7). This is because TLV mainly removes water from the third space, thereby preserving the renal hemodynamics and renal function (8). Arginine vasopressin (AVP) binds to the V2 receptor of the basolateral membrane of the collecting duct and phosphorylate of aquaporin (AQP) 2, which is a water channel, through cyclic AMP. AQP2 present on the membrane vesicle is then moved to the luminal membrane, thereby enhancing the water permeability (Figure). Free water flows into the cell and is reabsorbed via the basolateral membrane through AQP3 and AQP4 (9). Activation of the V2 receptor

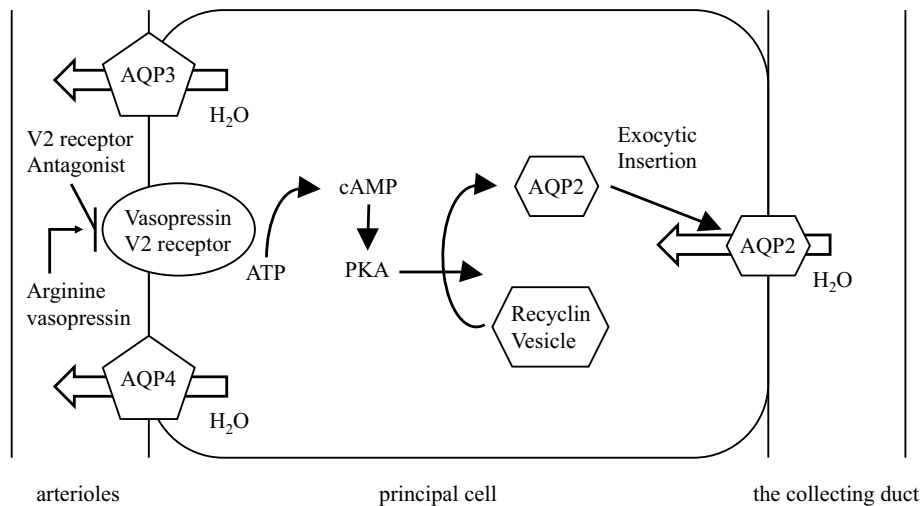


Figure. Diuretic Mechanisms of Tolvaptan. AQP: aquaporin, ATP: adenosine triphosphate, cAMP: cyclic adenosine monophosphate, PKA: protein kinase A

also reabsorbs Na^+ through the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter in the ascending limb of the loop of Henle, the Na^+/Cl^- cotransporter in the distal tubule and the epithelial Na^+ channel of the collecting duct principal cells (10). TLV selectively antagonizes the V2 receptor, promoting diuresis (mainly of free water) and thereby improving hyponatremia.

Vasopressin and Chronic HF

AVP, a peptide neuroendocrine hormone secreted from the posterior pituitary gland, has three receptors: V1a, V1b and V2. V1a and V2 receptors are involved in hemodynamics (11). V1a receptor is associated with vasoconstriction and cardiac hypertrophy, and the action of V2 receptor is as described above. Therefore, the enhancement of AVP increases afterload via the stimulation of V1a receptor and preload via the stimulation of V2 receptor (12). In HF, however, AVP secretion is increased by non-osmotic pathways enhanced by a reduction in cardiac output (cardiac index) and/or hyperactivated renin angiotensin aldosterone system (13). It has been reported that the AVP levels in patients with HF are higher than in healthy persons (14) and increase further as the New York Heart Association classification rises (15). Furthermore, the AVP level is increased even in asymptomatic patients with cardiac systolic dysfunction (16). It has also been reported that AVP is involved in cardiac remodeling after myocardial infarction (17). However, although the long-term use of TLV improved the volume overload, the long-term use of TLV was not found to be particularly beneficial (18). Therefore, these findings of TLV are not attributed to the hemodynamics, but they are due to the effects of neurohormonal factors induced by vasopressin. The effectiveness of the long-term use of TLV in all HF patients was denied by the large-scale EVEREST trial and a meta-analysis (19, 20). Similarly, conivaptan, a V1a and V2 receptor antagonist that is approved only in the USA, shows no long-term benefits (21). However, in pa-

tients with HF who maintain urine AQP2, the long-term use of TLV decreases the rates of death and re-hospitalization (22). A meta-analysis reported that the subgroup of patients with hyponatremia might have a better mortality outcome with TLV than without its administration (23). We also previously reported that the long-term use of TLV prolonged the period until re-hospitalization (24). Therefore, in some patients, the long-term use of TLV may affect the outcomes of HF. However, predicting which patients will enjoy such benefits is difficult at present, and further clinical studies are necessary.

Effectiveness of TLV for HF According to Clinical Trials

After Gheorghiadu first reported the effectiveness of TLV for chronic HF in 2003 (25), the large-scale EVEREST trial was conducted in 2007. In short-term trials of EVEREST, TLV increased diuresis and improved HF signs and symptoms in many patients (26). However, it has been reported that the use of TLV in the acute phase of HF significantly improved dyspnea and edema but had no effect on rales or pulmonary congestion (27). The backgrounds of subjects differed among these previous studies, though, so the QUEST trial on loop diuretics-resistant HF subjects was conducted in Japan (1). The administration of TLV for seven days increased the urine volume and improved HF symptoms in loop diuretics-resistant HF subjects. Based on these findings, TLV was approved in Japan for HF patients suffering from fluid retention despite receiving the standard treatment with conventional diuretics. Since the effectiveness of TLV depends on individual patients, it is important to consider ways to determine which HF patients will benefit the most from TLV. For example, the collecting duct function must be preserved in these patients, as TLV exerts its effect at the collecting duct. However, stress tests, such as the Fishberg concentration test, are not suitable for HF patients

Table. Characteristics of Studies Regarding the Effectiveness and Safety for Early Use of Tolvaptan.

Reference	Subjects	Country	No. of patients (% of Male)	Age (Years) mean (S.D.)	LVEF (%) mean (S.D.)	Timing of initiation of TLV from hospitalization or operation	Main outcomes
38	Underwent cardiac surgery with cardiopulmonary bypass	Japan	T: 147 (61.9) C: 133 (55.6)	T: 70.8 (11.4) C: 69.5 (12.2)	T: 62.9 (10.5) C: 62.5 (10.1)	Within 24 hours	body weight, renal function
35	ADHF	Japan	T: 31 (48.4) C: 25 (56.0)	T: 85.5 (4.5) C: 86.7 (5.3)	T: 44.6 (16.9) C: 44.2 (13.0)	Within 24 hours	body weight, renal function, hospital stay
36	ADHF	Japan	E: 67 (44.7) NE: 35 (77.1)	E: 85.0 (5.6) NE: 61.3 (9.4)	E: 57.1 (15.3) NE: 44.3 (20.9)	NA	renal function, hospital stay, mortality rate
34	ADHF	Japan	247 (58.2)	74.0 (11.9)	47.7 (18.8)	NA	hospital stay
37	ADHF	Japan	VE: 45 (42.2) NVE: 45 (68.2)	VE: 89 NVE: 74	VE: 49 NVE: 44	Within 24 hours	renal function, hospital stay, in-hospital death
33	AHF and renal dysfunction or hyponatremia; or diuretic resistance	United States	T: 122 (75.4) C: 128 (72.7)	T: 70 (11) C: 67 (13)	T: 35 (16) C: 33 (17)	Within 36 hours	dyspnea, body weight, renal function, death or re-hospitalization within 30 days
40	ADHF	Japan	T: 26 (38.5) C: 26 (46.2)	T: 80.5 (12.2) C: 86.2 (5.0)	T: 47.5 (16.8) C: 56.7 (11.5)	Within 24 hours	renal function, death or re-hospitalization within 90 days
32	ADHF	Japan	R: 77 (61.0) NR: 12 (48)	R: 76.7 (13.6) NR: 77.3 (12.5)	R: 53.8 (18.0) NR: 49.2 (19.3)	NA	tolvaptan response, cardiac rehabilitation, hospital stay, in-hospital death
39	Underwent cardiac surgery with heart valve surgery	Japan	T: 39 (56.4) C: 42 (54.8)	T: 68 (12) C: 66 (14)	T: 59.4 (15.9) C: 51.6 (19.0)	NA	body weight, serum sodium
31	AHF	Japan	T: 52 (76.9) C: 131 (58.0)	T: 75 C: 77	T: 40 C: 32	Within 12 hours	Renal function, death within 6 months

LVEF: Left Ventricular Ejection Fraction, S.D.: standard deviation, TLV: Tolvaptan, T: Tolvaptan group, C: Conventional group, E: Elderly group, NE: Elderly group, VE: Very elderly group, NVE: Non-very elderly group, AHF: acute heart failure, R: Response group, NR: Non-response group

in the acute phase. If the collecting duct function is maintained, AVP levels elevated by HF promote AQP2 expression, and the urinary AQP2 excretion also increases. Urinary AQP2 levels are reported to predict the effectiveness of TLV (22). However, measuring urinary AQP2 is not generally performed in the routine clinical setting. Urine osmolality has also proven useful for evaluating the efficacy of TLV (28, 29), as has the ratio of AVP and the plasma aldosterone concentration (30).

Effectiveness of TLV for Treating HF in the Acute Phase

The renal function tends to decrease in the acute phase of HF treatment, although it is necessary to start TLV during hospitalization. In such cases, the renal function in these patients may be preserved by TLV, as mentioned above. Besides, the timing of the start of TLV after hospitalization is drawing attention, now. We summarized the outcomes of the

early use of TLV for acute HF in Table. Shirakabe et al. reported that the early use of TLV ameliorated the renal function deterioration and improved the mid-term prognosis of HF (31). In addition, the early use of TLV for HF reduced the rate of in-hospital death (32, 33) and shortened the hospital stay (34). These effects were similarly reported in elderly patients (35-37) and after cardiac surgery (38, 39). The use of TLV within two to four days after hospitalization was classified as “early” in these retrospective studies.

There have been many prospective studies describing the outcomes of starting TLV within 24 hours after hospitalization (40). However, another point must be borne in mind: TLV was only approved for use in HF patients suffering from fluid retention despite receiving the standard treatment with conventional diuretics (1). Therefore, we must carefully consider patient background characteristics, although the early use of TLV after hospitalization is indeed useful. It has been reported that additional treatment of TLV is useful for HF patients in whom loop diuretics were originally adminis-

tered but later developed resistance (41). The early use of TLV for acute exacerbation of chronic HF may also be effective. In addition to loop diuretics, the relationship between human atrial natriuretic peptide or thiazide and TLV has been investigated (42, 43). In a recent study, sodium-glucose cotransporter (SGLT) 2 inhibitor, which is a new therapeutic medication for diabetes mellitus, also attracted attention as a treatment for HF with diuretics action (44), and clinical trials are being conducted. However, which combination of TLV and other diuretics, including SGLT2 inhibitor, is the most effective remains unclear, so further clinical studies are necessary.

Safety of TLV

The patient's serum sodium concentration and ability to feel thirsty (or whether or not patients are able to drink) should be carefully monitored (1). It is recommended that the serum sodium concentration be evaluated before TLV administration, at 4 to 6 hours after TLV administration, at 8 to 12 hours after TLV administration and the next day. Clinical data accumulated over the seven years since TLV entered the market [post-marketing surveillance (Samsca Post-Marketing Surveillance In Heart Failure: SMILE study)] highlighted important clinical points concerning when to start TLV and the serum sodium concentration. It was reported in the SMILE study that the risk of hypernatremia increases when the serum sodium concentration exceeds 142 mEq/L and the serum potassium concentration is less than 3.8 mEq/L before the administration of TLV (45). Therefore, TLV should be initiated at a low dose in patients with a high risk of hypernatremia. In addition, it has been reported that the incidence of hypernatremia is increased in patients ≥ 80 years of age compared with those < 80 years of age (46). However, the long-term use of TLV (for more than 15 days) reportedly does not increase the risk of hypernatremia (47). The safety and effectiveness of using TLV for children has been reported as well (48), so hypernatremia may be able to be avoided by the long-term use of TLV if we identify groups at high risk of hypernatremia and initiate TLV at relatively low doses, such as 3.75 mg/day. Although a meta-analysis reported in 2017 that TLV was not associated with an increased risk of adverse events (49), one report has claimed that the long-term use of TLV increased the risk of adverse events by 14% (20). The risk of adverse events should be evaluated when considering the continued use of TLV (especially in the long term).

Conclusion

We outlined the effectiveness and safety of TLV. TLV is useful for many HF patients (including long-term use). However, many points remain unclear, such as how to identify which patients will most benefit from TLV. The accumulation of more evidence supporting the appropriate use of TLV is needed.

The authors state that they have no Conflict of Interest (COI).

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