Cardiovasc Prev Pharmacother. 2021 Jan;3(1):10-14
https://doi.org/10.36011/cpp.2021.3.e3
eISSN 2671-700X

Special Article

Check for updates

Vasopressin Receptor Antagonist, Tolvaptan, for Treating Hyponatremia in Patients with Heart Failure

Kyung-Jin Kim, MD

Division of Cardiology, Department of Internal Medicine, Ewha Womans University Medical Center, Ewha Womans University School of Medicine, Seoul, Korea

OPEN ACCESS

Received: Dec 26, 2020
Accepted: Jan 17, 2021

Correspondence to
Kyung-Jin Kim, MD
Division of Cardiology, Department of Internal Medicine, Ewha Womans University Medical Center, Ewha Womans University School of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea.
E-mail: kyungjinkimkorea@gmail.com

ORCID iDs
Kyung-Jin Kim
https://orcid.org/0000-0002-5796-3284

Conflict of Interest
The author has no financial conflicts of interest.

ABSTRACT

Hyponatremia is common in hospital setting in patients with heart failure and is associated with increased morbidity and mortality. However, despite these complications, appropriate treatment strategies other than established therapies such as hypertonic saline, loop diuretics, and fluid restriction are limited. Tolvaptan, a vasopressin receptor antagonist, has aquaretic effects that excrete free water and dilutes urine, thereby increasing serum sodium concentration. This new approach might be a landmark in the treatment of hyponatremia as there is a lack of controlled studies in this field. However, regardless of the associated advantage, tolvaptan is recommended to be used for less than 30 days owing to the possibility of liver injury. This study is aimed to present the clinical use of tolvaptan for hyponatremia in patients with heart failure.

Keywords: Antidiuretic hormone receptor antagonists; Heart failure; Hyponatremia; Tolvaptan; Vasopressins

DISCOVERY OF VASOPRESSIN

An interesting discovery study was reported in the year 1985 on the secretion from the pituitary gland that not only raises blood pressure,[1] but also reduces urine production.[2] This substance is synthesized in the anterior hypothalamus and is secreted into the posterior pituitary and named as vasopressin.[3] Purification of vasopressin and identification of its amino acid[4] was followed by isolation of the gene and molecular cloning of its receptors: V_{1a}, V_{1b}, and V_2.[5][6] The V_{1a} receptor is found in smooth muscle, myocardium, hepatocytes, platelets, and brain, resulting in vasoconstriction, myocardial hypertrophy, glycogenolysis, and platelet aggregation. The V_{1b} receptor is associated with the secretion of corticotropin. The V_2 receptor is located in the collecting duct cells that results in repositioning of the water channel to the apical cell membrane.[7]

HYPONATREMIA IN PATIENTS WITH HEART FAILURE

Hyponatremia in patients with heart failure (HF) is common and is associated with an increased risk of morbidity and mortality.[8] It is caused by multifactorial reasons, but

primarily from decreased cardiac output, which increases the level of vasopressin. The increased production of vasopressin is either due to decreased circulating volume in the artery, which stimulates the arterial baroreceptor, or by dysregulation that elevates the level of vasopressin despite arterial distension, increased blood volume, and low plasma osmolality.[9] In patients with HF, increased vasopressin level especially affects the V_{1a} and V_2 receptors. The activation of V_2 receptor causes reabsorption of free water from the renal collecting ducts, and that of V_{1a} receptor causes vasoconstriction to raise blood pressure.[10] The mechanism of action of vasopressin via V_2 receptor in hyponatremia is worth describing in detail. When vasopressin combines with the vasopressin receptor of the collecting ducts, the activated receptor stimulates adenylyl cyclase to generate cyclic adenosine monophosphate (AMP); cyclic AMP activates protein kinase A, which is an enzyme that phosphorylates the aquaporin water channels. After phosphorylation, aquaporin translocates from the inside of the cell to the surface membrane of the collecting ducts. It then reabsorbs free water from the lumen of the collecting duct back into capillaries, thereby resulting in more concentrated urine in the collecting ducts and increase in free water in the body, and subsequently a lower serum concentration of sodium.[3] Despite the prevalence and clinical implication of hyponatremia in patients with HF, established therapies such as hypertonic saline, loop diuretics, and fluid restriction have several limitations including inadequate blood volume status, electrolyte imbalance, and compliance issues.[11] Therefore, the use of vasopressin receptor (V_2) antagonist as a treatment strategy might have potential in regulating free water in patients with HF.

TOLVAPTAN, VASOPRESSIN RECEPTOR ANTAGONIST

Tolvaptan is a vasopressin receptor antagonist that inhibits the V_2 receptor and results in the suppression of reabsorption of free water, causing excretion of diluted urine and therefore, concentration of sodium in the blood increases.[3] The efficacy and safety of tolvaptan were evaluated in previous trials, including that in the Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT trial),[12] Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST trial),[13] and Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions (SALTWATER study).[14] In 2006, Schrier et al.[12] reported a multicenter randomized study comparing the efficacy of tolvaptan to placebo in patients with euvolemic or hypervolemic hyponatremia: serum sodium <135 mmol/L (SALT trial). Patients involved in the study had syndrome of inappropriate antidiuretic hormone secretion (SIADH), cirrhosis, or chronic HF in association with hyponatremia [12]. Primary endpoints were change in the average under the curve (AUC) for the serum sodium concentration from baseline to day 4, and the change from; both the endpoints were achieved without significant side effects. However, hyponatremia recurred during the week after discontinuation of tolvaptan on day 30.[12] Continually, tolvaptan was evaluated in larger number of patients for a longer duration (median follow-up of 9.9 months), who were hospitalized due to HF in 2007 (EVEREST trial).[13] The EVEREST trial was an event-driven randomized controlled study in which the primary outcome was a composite of all-cause mortality, cardiovascular death, and HF hospitalizations. Although tolvaptan did not improve HF-related morbidity and long-term mortality rates associated with acute HF syndrome, the serum sodium level increased significantly. Conforming to these results, tolvaptan was approved by the Food and Drug Administration (FDA) in 2009 for the treatment of clinically significant hypervolemic and euvolemic hyponatremia. Later, in 2010, Berl et al.[14] conducted an open-label extension

https://doi.org/10.36011/cpp.2021.3.e3

study of the SALT trial. This SALTWATER trial demonstrated the maintenance of serum sodium concentration with prolonged administration of tolvaptan in patients with chronic hyponatremia, with an acceptable safety.[14]

Hence, tolvaptan may effectively increase the level of serum sodium without improving long-term outcomes. Tolvaptan can be considered for regulating free water in the body in patients with hyponatremia and HF, without survival benefit. Compared to other diuretics, especially the most commonly used loop diuretics, tolvaptan only releases free water into the collecting ducts, but loop diuretics create a diuretic effect by inhibiting the Na-K-2Cl symporters in the ascending limb of the loop of Henle.[15] The mechanism of action of loop diuretics can cause diuretic resistance, renal dysfunction, and electrolyte imbalance. Moreover, one study discovered that the use of loop diuretics reduced renal blood flow to a greater extent than that did tolvaptan.[16] Therefore, despite the lack of survival benefit, tolvaptan can be considered an effective treatment in patients with hyponatremia and HF due to the advantages of its specific mechanism.

USE OF TOLVAPTAN

Tolvaptan has a half-life of 6–8 hours and maximum effect at 2 hours after administration. Metabolism is mainly carried out by the cytochrome P-450 isoenzyme CYP3A4 present in liver, and the amount of excretion in urine is less than 5%.[3] The initial recommended dose is 15 mg per day, and if necessary, the dose can be increased up to 60 mg per day at intervals of 24 hours or more, depending on the serum sodium concentration. Drug titration is better to be performed while the patient is being hospitalized, since it is necessary to check the initial serum sodium level concentration for drug dosage adjustment. If serum sodium correction is made quickly, neurologic sequelae may occur. Therefore, it is not recommended to advice water restriction in parallel during the initial 24 hours of drug administration, as it may have additive effect in the correction of serum sodium level. For a similar reason, close monitoring of serum sodium level is also critical when using diuretics.[17]

If the serum sodium level rises too quickly, it can lead to osmotic demyelination syndrome, though no actual cases were reported in the SALT trial,[12] the SALTWATER study,[14] and the EVEREST study[13] in patients with rapid correction of serum sodium. However, several cases have been reported of osmotic demyelination syndrome, including one case in which the reason was rapid increase in serum sodium level from 122 to 167 mM/L[18] and, the other two cases in which 3% solution was used together.[19]

ADVERSE EVENTS

Symptoms such as polyuria, frequent urination, thirst, dry mouth, and constipation were reported more frequently in patients receiving tolvaptan than those in in the placebo group.[3] Similarly, in the EVEREST study, symptoms such as thirst and nausea were reported more frequently in the tolvaptan group than that in the placebo group.[13] However, in a study involving patients with autosomal dominant polycystic kidney disease (ADPKD), the use of tolvaptan caused an increase in liver enzymes, and two of the participating patients were withdrawn due to liver injury. Consequently, the FDA recommended tolvaptan to be used for less than 30 days, especially in patients with liver disease. One study attempted to review the data of an earlier study involving patients with ADPKD to examine the characteristics

https://doi.org/10.36011/cpp.2021.3.e3

of liver injury.[20] The study revealed that hepatocyte damage in patients with ADPKD began 3 to 18 months after drug administration, and gradually improved from 1 to 4 months after discontinuation of the drug. None of these patients progressed to liver failure or chronic liver injury.[20] This study aimed to further evaluate other long-term studies using tolvaptan in patients without ADPKD, and did not observe similar risk of liver injury in patients with HF, cirrhosis, or hyponatremia.[20] Conclusively, the authors speculated that ADPKD patients are more susceptible to liver injury with the use of tolvaptan due to an unknown pathology.[20] Meanwhile, in 2017, tolvaptan was tested in patients with later-stage ADPKD over a period of one year and resulted in a slower decline of the estimated glomerular filtration rate.[21] As a result, the FDA approved the use of tolvaptan in adults at risk of rapidly progressing ADPKD in 2018, to help slow the decline in kidney function. However, until now, tolvaptan has not effectively reduced overall mortality, cardiovascular mortality, or HF hospitalizations. Further studies to evaluate the safety and long-term benefits of tolvaptan should be conducted.

CONCLUSION

Tolvaptan, a vasopressin receptor antagonist, may be a milestone in the treatment of hyponatremia with the advantage of regulating free water in the body. Although tolvaptan is not associated with survival benefits and risks neurological complications and liver toxicity, tolvaptan can be considered for treatment in patients with hyponatremia and HF if it is used with caution and is closely monitored.

REFERENCES

1. Oliver G, Schäfer EA. On the physiological action of extracts of pituitary body and certain other glandular organs: preliminary communication. J Physiol 1895;18:277-279.
PUBMED | CROSSREF
2. Von den Velden R. Die nierenwirkung von hypophysenextrakten beim menschen. Berlin Klin Wochenshr 1913;50:2083-6.
3. Berl T. Vasopressin antagonists. N Engl J Med 2015;372:2207-2216.
PUBMED | CROSSREF
4. Turner RA, Pierce JG, du Vigneaud V. The purification and the amino acid content of vasopressin preparations. J Biol Chem 1951;191:21-28.
PUBMED | CROSSREF
5. Birnbaumer M, Seibold A, Gilbert S, Ishido M, Barberis C, Antaramian A, Brabet P, Rosenthal W. Molecular cloning of the receptor for human antidiuretic hormone. Nature 1992;357:333-335.
PUBMED | CROSSREF
6. Thibonnier M, Auzan C, Madhun Z, Wilkins P, Berti-Mattera L, Clauser E. Molecular cloning, sequencing, and functional expression of a cDNA encoding the human V1a vasopressin receptor. J Biol Chem 1994;269:3304-3310.
PUBMED | CROSSREF
7. Ali F, Guglin M, Vaitkevicius P, Ghali JK. Therapeutic potential of vasopressin receptor antagonists. Drugs 2007;67:847-858.
PUBMED | CROSSREF
8. Donzé JD, Beeler PE, Bates DW. Impact of hyponatremia correction on the risk for 30-day readmission and death in patients with congestive heart failure. Am J Med 2016;129:836-842.
PUBMED | CROSSREF
9. Rodriguez M, Hernandez M, Cheungpasitporn W, Kashani KB, Riaz I, Rangaswami J, Herzog E, Guglin M, Krittanawong C. Hyponatremia in heart failure: pathogenesis and management. Curr Cardiol Rev 2019;15:252-261.
PUBMED | CROSSREF

https://doi.org/10.36011/cpp.2021.3.e3

10. Rosner MH. Hyponatremia in heart failure: the role of arginine vasopressin and diuretics. Cardiovasc Drugs Ther 2009;23:307-315.
PUBMED | CROSSREF

11. Filippatos TD, Elisaf MS. Hyponatremia in patients with heart failure. World J Cardiol 2013;5:317-328.
PUBMED | CROSSREF

12. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C; SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099-2112.
PUBMED | CROSSREF

13. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. JAMA 2007;297:1319-1331.
PUBMED | CROSSREF

14. Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, Czerwiec FS; SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol 2010;21:705-712.
PUBMED | CROSSREF

15. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21:137-155.
PUBMED | CROSSREF

16. Costello-Boerrigter LC, Smith WB, Boerrigter G, Ouyang J, Zimmer CA, Orlandi C, Burnett JC Jr. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. Am J Physiol Renal Physiol 2006;290:F273-F278.
PUBMED | CROSSREF

17. Epperla N, Landeck J, Sabbagh S. Osmotic demyelination syndrome. WMJ 2014;113:197-198.
PUBMED

18. Malhotra I, Gopinath S, Janga KC, Greenberg S, Sharma SK, Tarkovsky R. Unpredictable nature of tolvaptan in treatment of hypervolemic hyponatremia: case review on role of vaptans. Case Rep Endocrinol 2014;2014:807054.
PUBMED | CROSSREF

19. Lehrich RW, Ortiz-Melo DI, Patel MB, Greenberg A. Role of vaptans in the management of hyponatremia. Am J Kidney Dis 2013;62:364-376.
PUBMED | CROSSREF

20. Watkins PB, Lewis JH, Kaplowitz N, Alpers DH, Blais JD, Smotzer DM, Krasa H, Ouyang J, Torres VE, Czerwiec FS, Zimmer CA. Clinical pattern of tolvaptan-associated liver injury in subjects with autosomal dominant polycystic kidney disease: analysis of clinical trials database. Drug Saf 2015;38:1103-1113.
PUBMED | CROSSREF

21. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Koch G, Ouyang J, McQuade RD, Blais JD, Czerwiec FS, Sergeyeva O; REPRISE Trial Investigators. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med 2017;377:1930-1942.
PUBMED | CROSSREF