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TORASEMIDE FOR THE TREATMENT OF HEART FAILURE

Cardiology

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ABSTRACT

Diuretics play a major role in the first line treatment for the Congestive Heart Failure (CHF). These diuretics are currently and majorly used for symptomatic relief. Torasemide, a loop diuretic, is a newly developed loop diuretic, which has a longer half-life, longer duration for action, and higher bioavailability as compared to the other loop diuretics like furosemide. Torasemide, also works more effectively for the anti-aldosterone effect and vasorelaxation effect. Several studies have also suggested that torasemide has superior pharmacokinetics and pharmacological activities than that of furosemide. Results of several studies state that torasemide helps in improving the left ventricular function, reduces the mortality, as well as the frequency and duration of heart failure. Torasemide also improves the quality of life, tolerance and NYHA functional class in patients suffering from CHF. Based on these results, torasemide appears to be a promising loop diuretic for the first line treatment and for better management of the patients with CHF. In this review, we provide a panorama of existing knowledge on the properties of torasemide, aimed at using it as a first line of treatment for the patients in Congestive Heart Failure (CHF).

KEYWORDS

Torasemide, Congestive Heart Failure, Cardiological Perspective, Anti-aldosterone Effect, Vasodilatory Effect.

INTRODUCTION

Loop diuretics are the major key player for the symptomatic treatment of the Congestive Heart Failure (CHF) [1]. These are currently recommended to treat CHF [2,3]. The first developed loop diuretic, Furosemide, is most commonly used and widely prescribed loop diuretics in CHF treatment. Many attempts were made to develop the alternative and better loop diuretics than the furosemide. A subsequent version of loop diuretic was made with ethacrynic acid, bumetanide and piretanide, which could not perform better than furosemide [4]. A clinical trial in the recent year demonstrated a loop diuretic called torasemide. Torasemide has remarkable pharmalogical profile than that of the currently used loop diuretic, Furosemide. Torasemide has better clinical outcomes and fast symptom relief during the treatment for CHF, than that of furosemide. As a result of the better outcomes, torasemide can be considered as better loop diuretic than that of furosemide. Emphasing on the pharmacological properties of torasemide. This Review aims at providing the therapeutic potential of torasemide with its basic and clinical aspects for the treatment of CHF.

PHARMACOLOGICAL PROPERTIES

In the region of the thick ascending limb of loop of Henle, NaCl reabsorption is controlled by a cotransport system known as Na+/2Cl-/K+. This cotransport system is present in the luminal membrane of the loop of Henle. Loop diuretics bind to this carrier protein in reversible manner so that there is reduction or abolishment of NaCl reabsorption [4]. This leads to interstitial hypertonicity, which further causes reduced water reabsorption. On another hand, this loop diuretics increases the urinary K+ excretion and reduces the K+ reabsorption in the loop of Henle, by enhancing the distal tubular K+ secretion. Just like the working mechanism of furosemide, torasemide acts on the peritubular side of nephron, by interfering in the Cl- channels of the basolateral membrane, which further reduces the rate of Cl- reabsorption [5].

Many experiments and clinical settings were performed and were explored for pharmacodynamics and Pharmacokinetics of Torasemide. Previous studies on the effects of Intravenously and Orally administrated torasemide have shown similar results of plasma concentration-time curves (AUC). These curves results were independent studies between Intravenous administration and Oral Administration [6,7]. In a study exploring for bioavailability of torasemide, similar results were found, where it presented 80-90% of bioavailability in each case [8-11]. These results suggest that high bioavailability of torasemide indicates that the first-pass effects must be almost negligible, which states that torasemide has extreme lipophilic properties [12] or high protein-binding affinity [7].

Some studies have also indicated that torasemide has a rapid rate of absorption and is merely affected by food intake [10], and this has a relatively long half-life of 3-4 hours. As a result, torasemide has a longer duration of natriuretic action of nearly 6-8 hours [8-11]. Pharmacodynamics evaluated studies showed that relationship between the urinary sodium excretion rate vs the diuretic excretion rate of torasemide rate shifted to more left than furosemide, making torasemide a potent loop diuretic than that of furosemide [9-11]. In the study comparing the milligram dosing on the basis of diuretic and natriuretic effects showed that torasemide is 4-6 times better than furosemide [9-13]. It has been observed that patients with CHF, tend to have minimized absorption rate and diuretic effects, thus the loop diuretics like bumetanide or furosemide do not work functionally, whereas, torasemide could perform well in the same conditions [14,15]. Some previous studies demonstrated that both the rate of absorption and pharmacodynamic effect of furosemide, completely differ in the patients having compensated and decompensated CHF [16], making the treatment of oedema in CHF more challenging.

In a study evaluating the bioavailability, pharmacodynamics and pharmacokinetics of torasemide and furosemide in a randomized crossover trial in 16 patients. They stated that Maximum Plasma Concentration (Cmax) and Transport Maximum (tmax) of orally administrated torasemide in patients with CHF versus the healthy patients has the same effective effect with no great difference [17]. This study totally challenges the effective working of furosemide, of which the absorption level is significantly delayed in CHF [14-16]. The bioavailability of loop diuretic torasemide in the CHF patients is just about 90%, which is significantly greater than those of the healthy patients, who are administrated with Furosemide [17]. In a study, it showed that there was significantly less variability in the factors like bioavailability of torasemide (coefficient of variation; 9%) versus furosemide (coefficient of variation; 30%) [17]. In a new study, patients were examined for their heart failure status in conditions like compensated versus decompensated influences in the setting of pharmacodynamics and pharmacokinetics of torasemide.

They evaluated in 12 patients that the oral administration of 100mg torasemide, causes the hemodynamic parameters and clinical signs along with symptoms were resolved in decompensated heart failure. Study results significantly demonstrated that decompensated heart failure status will cause decrease in Cmax and an increase in tmax, which has a true decrease in AUC.

Furthermore, these results of studies do not change the maximum urinary excretion rate, stating that the heart failure does not affect the pharmacodynamics of torasemide. In the final conclusion, with contrast to furosemide, torasemide seems to be a much more potential loop diuretic that holds a true pharmacodynamic and pharmacokinetic actions, with or without the patients having CHF. The pharmacological features of Torasemide are summarized in Table 1.

ANTI-ALDOSTERONE EFFECTS

Anti-aldosterone effect is the most prominent feature of torasemide that makes it better from any other loop diuretics available. In a study presented in 1991, it showed for the first time that the torasemide inhibited the binding of aldosterone to its receptors in cytoplasmic fraction of rat kidney in a very dose dependent manner [19].

Table 1. pharmacological features of Torasemide

1. Pharmacological Properties
• Higher absorption rate which cannot be influenced by CHF. • Higher rate of bioavailability near to 90%. • Less variability in bioavailability • Stable pharmacodynamic properties, even in CHF.
2. Anti-aldosterone Effect
• Improves the myocardial fibrosis by activating the anti-aldosterone effect. • Preventing the tolerance phenomenon by inhibiting the upregulation of Na+ • Increasing the left ventricular function and preventing its remodeling. • Reduction in cardiac sympathetic nerve activities.
3. Vasodilatory actions
• Increased secretions of prostacyclin or Nitric Oxide from endothelial cells. • Inhibition of Angiotensin II and endothelin-1-induced vasoconstriction.
4. Other Properties
• Increased Quality of Life, reduced frequency of urination. • Improvement in exercise tolerance • Reduction in Plasma brain natriuretic peptide. • Reduction in the frequency and the duration of heart failure • Reduced Mortality Rate.

On the other hand, in the same study, furosemide did not produce any such effect. This effect directly decreased the urinary excretion of potassium by torasemide as compared to that of furosemide, as observed in the same study and the other studies reported the same results later [9, 19]. The anti-aldosterone effect of torasemide also affects the heart. First, the mineralocorticoid receptors are also available in cardiomyocytes, endothelial cells and fibroblasts of human heart [20-22]. Second, aldosterone is secreted from adrenal gland, which also stimulates the cardiac collagen synthesis and fibroblast proliferation by activating the mineralocorticoid receptors [23-26].

In a study, patients were tested for whether torasemide could inhibit the aldosterone binding in heart by examining the trans cardiac extraction of aldosterone in patients with CHF who were administrated with furosemide and torasemide. In the results of Furosemide, the aldosterone level in plasma concentration in coronary sinus was much lower than that of aorta [27]. But in the case of torasemide there was no significant difference in the plasma concentration level between the coronary sinus and the aorta. On another hand, Plasma level concentration of procollagen type III aminoterminal peptide (PIIP) which is an important biomarker for the fibrosis, were higher in the furosemide group than that of the torasemide group. These results suggest that furosemide lacks and torasemide has an aldosterone receptor antagonist action in the heart. These antagonist receptors may improve the myocardial fibrosis in CHF. These results were same in the other study by the same group, which showed that aldosterone antagonist and spironolactone were inhibited by the transcardiac extraction of aldosterone with many positive effects between the transcardiac concentration of plasma aldosterone and PIIP in CHF Patients [28].

This Inhibitory effect action of the torasemide binding to its receptor, the anti-aldosterone effect is currently just studied on rats, cows and guinea pigs' adrenal cells in vitro condition, thus they successfully show the inhibitory concentrations for adrenal cells than those of the invitro isolated renal tubules [29]. Also, the data regarding the in vivo human of this effect is not studied in recent, so remains unavailable and needs to be studied further with specific clinical trials.

Furthermore, it is seen that using the loop diuretic for a long period of time, can lead to decreased diuretic effect [30]. This phenomenon is known to be loop diuretic resistance or tolerance. This occurs due to increase in the Na+ transporters in the site of action of the loop diuretics. This also increases because of an increase in the Thiazide-sensitive Na+/Cl- cotransporter (TSC) of the Distal Convoluted Tubule (DCT) and epithelial NA+ Channel (ENaC) of the collecting tubules [31,32]. The anti-aldosterone effect of torasemide still needs clinical trials to evaluate its significance and clarity in the same.

VASODILATORY EFFECTS

Some studies suggest that torasemide effects the blood pressure by reducing it, even when administrated in a small dosage. These effects do not suggest natriuresis but directly suggests the involvement of vasodilatory action of torasemide [33, 34]. In mechanism, there is more secretions of Prostacyclin [35] or nitric oxide [36] in the endothelial linings and their secondary messengers like cAMP and cGMP [37] which catalyses' the vasodilatory effect. In the same effect of vasorelaxation, torasemide can also suppress the vascular responsiveness to vasoconstrictive compounds. In the recent study, it was demonstrated that torasemide inhibits the angiotensin II- and endothelin-1-induced vasoconstriction unlike furosemide, which blocks the calcium increase on smooth muscle cells in the aorta [38]. The inhibitory actions of torasemide are more likely to be involved on Cl- channels unlike furosemide [39]. In the case of patient in CHF, there is increased ventricular afterload, which directly contributes to development of heart failure [40], the vasodilatory effect of torasemide may be the certain way towards the treatment of CHF. These uses of torasemide with CHF and its vasodilatory effects requires more studies and is beyond the scope of this paper.

CLINICAL DATA

The pharmacological studies and the profile above tell that torasemide is the superior loop diuretic in comparison to the traditional ones like furosemide in the treatment of CHF. This viewpoints of pharmalogical data for torasemide has been tested many times clinically and was found correct with a good clinical outcome as of the other loop diuretics like Furosemide. It is clear that the higher the bioavailability and the less the variability of bioavailability of torasemide, the more the chances of favorable outcomes in the steady diuresis than that of furosemide. This could be proved on the basis of the study that showed that the body water and the body weight between the furosemide and torasemide had the significant difference [41]. In their study, they studied on 246 CHF patients, where patients were switched from 40mg of Furosemide to 5-20mg of torasemide in the Randomized double-blind manner. Body weight of the patients administrated with Torasemide, suddenly decreased. This dosing was then maintained for 48 weeks, which gave out favorable results like decrease in the pedal oedema and pulmonary congestion.

Due to long duration of elimination half-life, there is longer working duration of action of torasemide than that of furosemide and hence a better quality of life. Especially in the mechanism of working action and frequency of urination and urgency of urination. In a study presented with the quality of life with torasemide showed that patients administrated with torasemide had lesser urge for urination than those administrated with furosemide [42, 43]. Thus, taking torasemide has less complications and less social restrictions unlike furosemide. This may also be considered as better patient comfort, which may also decrease the number of decompensation and hospitalizations, which is very common among patients with CHF [44-46].

With favorable and beneficial pharmacokinetic properties, the anti-aldosterone effect of torasemide has attracted many researchers and physicians for its application in clinical settings. One such study called Randomized Aldosterone Evaluation Study (RALES) has explained that anti-aldosterone effect reduces the possibilities of mortality with the patients suffering from CHF [47]. In the previous studies it was seen that aldosterone plays important role in development of heart failure by activating the sympathetic mechanism, myocardial fibrosis and baroreceptors [48].

Many studies have already explained the role of myocardial collagen fibers accumulating while there is deterioration of Left Ventricular Function during CHF [49]. This also suggests that aldosterone plays a major role in myocardial fibrosis [50, 51]. To the fact, Torasemide helps significantly by decreasing the fraction of myocardial fibrosis. Contrarily, Furosemide does not have the same properties. It was

observed that Carboxy-terminal peptide of procollagen type I and the carboxy-terminal peptide of I had the significant decrease in levels after the use of Torasemide for 8 months [52].

In the treatment of CHF, there is also use of Angiotensin converting inhibitors and betablockers to avoid morbidity and mortality [3]. These are started to improve the ventricular function and neurohumoral profile, just like the plasma concentration of the Brain Natriuretic Peptide (BNP). These results were tallied by a recent study [53] In a study of 50 patients that were openly labelled in a trial, having a moderate CHF, they were switched from furosemide to torasemide, which resulted in improved Left Ventricular Function and BNP plasma levels in many of these patients [54].

Thus, Torasemide can be a better and much more potent loop diuretic and could give a better Quality of Life, improved Left Ventricular Function, Humoral Factor, and exercise tolerance. Torasemide can also be seen improving the cardiac sympathetic nerve activity and left ventricular remodeling in patients with CHF. In an open label randomized controlled trial, 234 patients were hospitalized for CHF [45], they were switched from furosemide to torasemide. Improved Quality of life and health was observed in these patients within a 12 month-follow up period. The study also demonstrated that torasemide administration subsequently reduce the duration of heart failure and reduced fatigue as compared to the furosemide patients. The study also demonstrated that long term use of torasemide could reduce the incidence of hypokalemia by 50%.

ADVERSE EFFECTS OF TO RASEMIDE

In the clinical trials for Torasemide, it was seen that torasemide has better efficacy than other loop diuretics. In the studies discussed above, most common adverse effect observed was as same that of the other diuretics in less significant way [43, 45, 46]. The common adverse effects were electrolyte disturbances, headache, dizziness, gastrointestinal disturbances and fatigue [43, 45, 46]. There are very rare adverse effects of torasemide unlike other loop diuretics. Torasemide rarely has a withdrawal syndrome. As a result, torasemide could be safely used if administrated properly and monitored for possible side effects.

CONCLUSION

To the conclusion, Torasemide is a drug of highly predictable pharmacokinetics, which could result in proper urination and other beneficial effects like anti-aldosterone effect could be favorable for the pathophysiology of CHF. Hence, we can say that torasemide is the better alternative for the treatment of CHF. Further detailed studies and proper investigation is required for the management of patients with torasemide.

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