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REVIEW

Torasemide Prolonged-Release: A Review of its use in the Management of Edema Associated with Congestive Heart Failure

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Abstract: Loop diuretics are currently recommended by scientific societies and associations of cardiology for treatment of symptoms of heart failure. Furosemide, which belongs to this pharmacological group, is the most commonly used in this disease. Torasemide prolonged-release is an equally effective alternative to furosemide for that purpose, although it is thought that, in patients with heart failure, torasemide has cardiac benefits beyond its diuretic effects. This is due to the ability of torasemide to inhibit the enzyme involved in the myocardial extracellular generation of collagen type I molecules (also known as procollagen type I carboxy—terminal proteinase (PCP)), so this drug could reverse myocardial fibrosis and reduce collagen type I synthesis in patients with CHF. Furthermore, torasemide is a very safe drug, as this molecule has mild and transient side effects.

Keywords: torasemide, congestive heart failure, furosemide, edema

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Introduction

Diuretics play an essential role in modern cardiovascular therapy, and are currently recommended for the treatment of congestive heart failure. Specifically, loop diuretics, such as furosemide, are the most important agents in the treatment of chronic heart failure. Torasemide can be administered for the treatment of oedema associated with congestive heart failure, kidney or liver disease and mild to moderate hypertension, either alone or combined with other antihypertensive drugs.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Torasemide is a furosemide-like loop diuretic. The main site of action of these diuretics is the medullary portion of the ascending limb of Henle's loop. This type of diuretics mainly inhibit the sodium/chloride/potassium co-transport pump from the luminal side of the cell (Fig. 1). This results in reduced interstitial hypertonicity, decreased water reabsorption (of water), and, ultimately, a pronounced natriuresis and diuresis, without significantly altering the glomerular filtration rate, renal plasma flow and acid—base.

Loop diuretics also reduce calcium and magnesium absorption, and increase potassium excretion. Relative to an equipotent diuretic dose of furosemide, torasemide Inmediate—Release (IR) produces more water and electrolyte excretion, but does not increase potassium loss to the same extent. This is due to the structural formula of torasemide, that interferes chloride channels in the basolateral membrane of the peritubular side, leading to fewer losses of potassium in contrast to furosemide.[1]

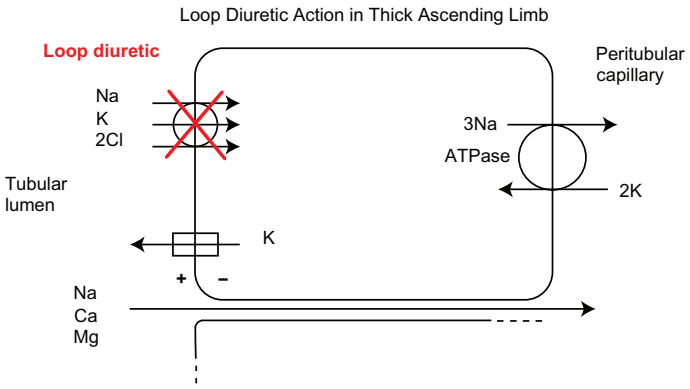

Figure 1. Mechanism of loop diuretic. This type of diuretics mainly inhibit the sodium/chloride/potassium co-transport pump from the luminal side of the cell.

Torasemide is rapidly absorbed after oral administration and reaches a maximal peak plasma concentration in the first hour. Its bioavailability is about 80%, and in contrast with furosemide, its intestinal absorption is not greatly influenced by simultaneous food intake. Furthermore torasemide shows little inter and intra—individual variation, allowing the change in the route of administration (oral and intravenous), no dosage adjustment is necessary. The tablet is absorbed with little first-pass metabolism, and elimination half-life in normal subjects is approximately 3.5 hours, being cleared from circulation by both hepatic metabolism (approximately 80% of the total clarification) and urine excretion (approximately 20% of the total clarification in patients with normal renal function).

In patients with normal renal function, 80% of the dose of torasemide undergoes extensive hepatic metabolism (specifically by the cytochrome P450 [CYP] 2C9 isoenzyme). The primary metabolite of torasemide is the biologically inactive carboxylic acid derivate. Although two of the other metabolites possess some diuretic activity, they are not considered to exert clinically significant diuretic effects as they do not attain sufficient concentrations in the urine. Approximetely 20% of the dose of torasemide is excreted in the urine as unchanged drug.

Several formulations of torasemida have been designed: immediate—release and prolonged—released formulations. For many years the original immediate-release (IR) formulation has been available worldwide. In order to facilitate a more gradual diuresis, a prolonged-release (PR) formulation of the drug, with an improved pharmacokinetic profile, has been recently developed. With the IR formulation, a rapid and vigorous diuretic effect is obtained over a period of several hours. Prolonged-released formulation might offer a more physiological diuresis, as it is designed to reduce the initial release of active substance in comparison to the standard IR formulation.

Figure 2 shows the mean plasma concentration versus time profiles for both PR and IR formulations after administration of a torasemide 5 mg dose.

As it can be seen, when we administer 5 mg of torasemide, greater concentration is reached with the IR-dose than with torasemide-PR, furthermore,

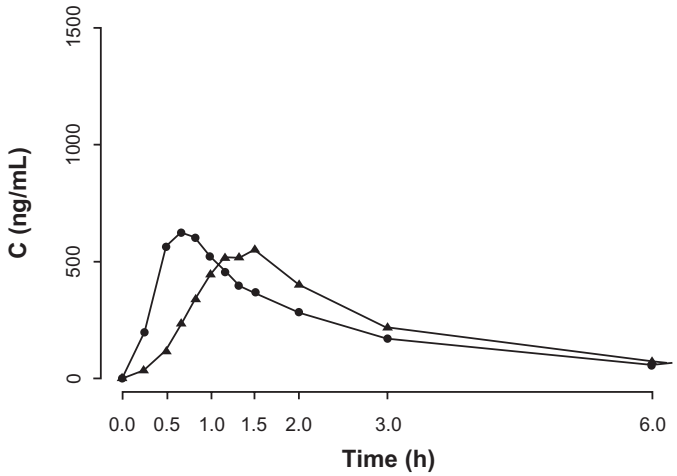

Figure 2. Farmacodinamic model in PR and IR formulations after the torasemide 5 mg dose.[2,3]

the peak plasma concentration is reached faster with IR-torasemide than with PR-torasemide. Then, torasemide remained detectable for at least 24 h with both formulations, but in the case of IR the urinary excretion was faster.[2,3]

In Figure 3, it is shown that the same behavior occurs when 10 mg of torasemide are given, as with IR—dose torasemide is obtained greater concentration than torasemide–PR dose, although the urinary excretion is faster. Then, torasemide remains detectable for at least 24 h with both formulations.[2,3]

We can affirm that for the torasemide 5 and 10 mg doses, the PR formulation exhibits a significantly lower and delayed plasma peak concentration compared with the IR formulation. This is typical of a prolonged–release form, represented by prolonged t_{max} and reduced C_{max}.

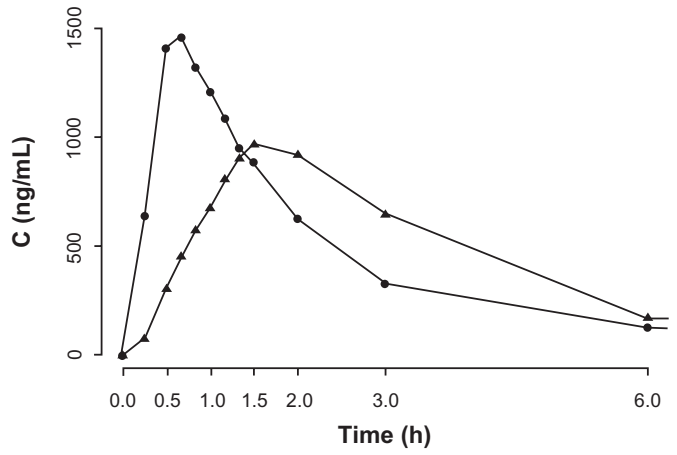

Figure 3. Farmacodinamic model in PR and IR formulations after the torasemide 10 mg dose.[2,3]

Therefore, diuretic and natriuretic responses are significantly different between the PR and IR formulation during the first 3 hours after administration, but not over the total 24–hour period. The IR formulation was associated with marked initial diuretic and natriuretic responses, with >50% of total natriuresis being produced within the first hours after administration, whereas the slower delivery of the PR formulation to the site of action led to relatively higher natiruretic efficiency and more constant diuresis.

Furthermore, torasemide—PR/IR may have an additional benefit beyond diuresis in patients with chronic heart failure, due to its supposed antifibrotic properties. In fact, research in rats and humans with heart failure have demonstrated that, whereas treatment with torasemide was associated with a reduction in the amount of histologically proven myocardial fibrosis (as assessed by measuring the collagen volume fraction), treatment with furosemide was not. This is related to the ability of torasemide to inhibit myocardial synthesis and deposition of collagen type I in patients with chronic heart failure, due to the inhibition of the Procollagen type I carboxy—terminal proteinase, an enzyme that metabolizes the synthesis and deposition of collagen in the myocardium. Molecular data show that torasemide interferes with the action of the myocardial enzyme procollagen type I C-terminal proteinase, which forms collagen type I molecules, and the myocardial enzyme lysyl oxidase, which, in turn, processes these molecules to form the final collagen type I fibers.

Clinical Studies

Several clinical trials show that torasemide is as effective as furosemide regarding diuretic effects for the treatment of heart failure symptoms such as edema. However, some differences suggest the possibility that torasemide has additional benefits in the treatment of this disease.

In recent decades the pathophysiological approach to heart failure has changed from the cardiorenal to the neurohumoral concept, and currently the interest is primarily focused on understanding the set of gene, molecular, cellular and interstitial changes that occur in the myocardium in HF and necessarily alter the size, shape and ventricular function (model of cardiac remodeling). One such change is related to the imbalance of the synthesis/degradation of the

extracellular matrix, particularly collagen fibers, which critically affect the myocardial structure, function and undertakes ventricular geometry.

In patients with heart failure, torasemide apparently has cardiac benefits beyond its diuretic effects. The deterioration of cardiac function in patients with HF of hypertensive origin involves myocardial fibrosis, which results from an increase in the synthesis and deposition of collagen type I fibres. Several studies have analysed whether the superior pharmacokinetic properties of torasemide have an impact on clinical outcome.

Muller K et al showed that patients with chronic heart failure treated with torasemide for 9 months gain a higher benefit in quality of life than furosemide tretated patients, due to torasemide's dual effect on both clinical status and social function; so, improvement in daily restrictions were significantly higher, number of mictions at 3, 6 and 12 h after diuretic intake and urgency to urinate significantly lower in torasemide—vs. furosemide-treated patients.[4] In the study of Murray MD et al patients treated with torasemide reduced both the frequency and the duration of HF—related hospitalisations compared with furosemide.[5] In the TORIC study, torasemide not only demonstrated that was more efficacious in improving NYHA class, but also was associated with a 51,5% reduction in mortality in comparison with furosemide/other diuretics.[6]

There are several clinical trials to evaluate the clinical effects of torasemide prolonged release in hypertension, which demonstrated that torasemide PR formulation showed noninferiority to torasemide IR in a randomized study. This work shows that 5 mg torasemide PR is not inferior than 5 mg of torasemide IR in the control of diastolic blood preseure (11,6 ± 7.1 mmHg, 95% confidence interval [CI] 10.6–12.5 to torasemide—PR and 11.3 ± 7.5 mmHg, 95% CI 10,2–12.3), furthermore, the proportion of patients who achieved adequate blood preasure control with PR formulation was significantly higher than with the IR formulation at 8 and 12 follow weeks.[7]

In the study of López et al, it was investigated whether torasemide inhibits the enzyme involved in the myocardial extracellular generation of collagen type I molecules (this enzyme is known as Procollagen type I carboxy—terminal proteinase [PCP]), and concluded that oral torasemide IR 10 or 20 mg/day reversed myocardial fibrosis and reduced collagen type I synthesis in patients with CHF, as evidenced by significant decreases from baseline in collagen volume fraction and serum carboxy—terminal propeptide of procollagen type I levels. This effect is due to the fact that torasemide has a capacity to inhibit procollagen type I carboxy–terminal proteinase (PCP), which is the enzyme involved in the myocardial extracellular generation of collagen type I molecules. Importantly, these beneficial effects on the reversal of myocardial fibrosis do not appear to be a class effect of loop diuretics, so, treatment with oral furosemide 20 or 40 mg/day is not associated with significant changes from baseline in PICP levels or PCP activation in these trials (In addition, torasemide-treated patients, but not furosemide-treated patients, showed decreased serum concentrations of the C-terminal propeptide of procollagen type I, a biochemical marker of myocardial fibrosis).[8]

TORAFIC (Coca et al), is a clinical large and randomized trial designed to test the efficacy of torasemide prolonged–release formulation in reducing myocardial fibrosis in chronic heart failure. In this trial 142 patients with chronic heart failure in New York Heart Association functional class II–IV were randomized to 8 months treatment with either torasemide—PR or furosemide. The primary objective is to test the hypothesis that torasemide—PR is superior to furosemide in reducing myocardial fibrosis and the primary outcome measurement is the difference in the change of serum propeptide of procollagen type I concentration from the initial to the final visit between both study groups. Results will be known at the end of 2009.[9,10]

Safety

The side effects of torasemide were generally mild and transient. Its most common adverse events were dizziness, headache, nausea, fatigue, muscle cramps, hypotension and gastrointestinal symptoms. Clinical studies with torasemide have demonstrated favorable safety profile, with no or minimal alterations of electrolyte and metabolic parameters (glucose, lipid values).[1]

Conclusions

As explained above, we can state that torasemide prolonged release is very useful in the treatment of congestive heart failure, due to its diuretic effect and its antiproliferative effect at the myocardium.

Moreover, compared to furosemide, torasemide has been shown to decrease both income and decompensation heart failure, and, at equal dose, torasemide prolonged-release reaches a lower and later peak plasma concentration, lasting longer than the immediate release formulation. Thus, diuresis would be maintained in a constant throughout the day, improving quality of life of these patients, who would not notice an urgent need to urinate during the first hours after taking the immediate release tablet.

Another beneficial effect of prolonged release torasemide in the treatment of chronic heart failure is its antiproliferative action based on the inhibition of the PCP enzyme (Procollagen type I carboxy—terminal proteinase), that decreases the myocardial extracellular generation of collagen type I molecules production, which influences the inhibition of negative remodeling of the ventricle that occurs in this disease. This effect could not be demonstrated so far with furosemide.[11,12]

Therefore, we are not dealing with mere diuretic for the treatment of edema associated to heart failure, but it is a drug that can influence the molecular, neurohormonal, cellular and interstitial changes that are launched at all based heart failure in an increased synthesis and function of angiotensin.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

References

1. Katherine A, Lyseng—Williamson, et al. Torasemide Prolonged Release. *Drugs*. 2009;69(10):1363–72.
2. Barbanoj MJ, Ballester MR, et al. Comparaison of repeated-dose pharmacokinetics of prolonged-release and immediate-release torasemide formulations in healthy young volunteers. *Fundam Clin Pharmacol*. 2009 Feb;23(1):115–25.
3. Barbanoj MJ, Ballester MR, et al. A bioavailability/bioequivalence and pharmacokinetic study of two oral doses of torasemide (5 and 10 mg): prolongedrelease versus the conventional formulation. *Clin Exp Pharmacol Physiol*. 2009 May–Jun;36(5–6):469–77.
4. Müller K, Gamba G, et al. Torasemide vs. furosemide in primary care patients with chronic heart failure NYHA II to IV—efficacy and quality of life. *The European Journal of Heart Failure*. 2003;5:793–801.
5. Murray MD, Deer MM, et al. Open label randomized trial of torasemide compared with furosemide therapy for patients with heart failure. *Am J Med*. 2001 Nov;111(7):513–20.
6. Cosín J, Díez J; TORIC investigators. Torasemide in chronic heart failure: results of the TORIC study. *Eur J Heart Failure*. 2002 Aug;4(4):507–13. Erratum in: *Eur J Heart Fail*. 2002 Oct;4(5):667.
7. Roca-Cusachs A, et al. Efectos clínicos de Torasemida de Liberación Prolongada en la hipertensión de leve a moderada: ensayo aleatorizado de no inferioridad frente a Torasemida de Liberación Inmediata. *Cardiovascular Therapeutics*. 2008;26(2):91–100.
8. López B, Querejeta R, et al. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. *J Am Coll Cardiol*. 2004 Jun 2;43(11):2028–35.
9. Coca A, de Teresa E, Beiras Alfonso C, et al. Evauation of the effects of prolonged-release torasemide versus furosemide on myocardial fibrosis (TORAFIC Study): design and baseline characteristics [abstract no. P-199]. *J Clin Hyper*. 2009 Apr;11(4 Suppl A):97.
10. Díez J, Coca A, de Teresa E, Anguita M, et al. TORAFIC study protocol: torasemide prolonged release versus furosemide in patients with chronic heart failure. *Expert Rev Cardiovasc Ther*. 2009;7(8):897–904.
11. López B, González A, et al. Identification of a potential cardiac antifibrotic mechanism of torasemide in patients with chronic heart failure. *J Am Coll Cardiol*. 2007 Aug 28;50(9):859–67.
12. Anguita M, Toledano F, León C, Castillo JC; Hipertensión arterial, cardiopatía hipertensiva e insuficiencia cardiaca. Papel de los diuréticos de asa. *Med Clin (Bard)*. 2008;131(17):660–4.