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Efficacy and safety of torasemide in patients with advanced renal insufficiency

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Abstract

Arterial hypertension and chronic kidney disease are major public health problems and closely interconnected. Thiazide and thiazide-like diuretics become less effective in advanced renal insufficiency and should be replaced by loop diuretics. However, studies negating that dogma exist in the literature. We conducted an observational retrospective study to evaluate the efficacy and safety of torasemide in patients with stage 3b chronic kidney disease who had uncontrolled blood pressure while receiving thiazide or thiazide-like diuretics. Thiazides were withdrawn, patients were administered torasemide, and follow-up was performed at 8-12 weeks post-torasemide initiation. Data were retrieved from medical records and analyzed retrospectively. A total of 24 patients (aged 67.1±6.1 years; 11 females) fulfilled all study criteria and were included in the analysis. Systolic blood pressure was substantially reduced following torasemide therapy (from 154.3±5.6 to 140.2±6.6 mmHg), and the reduction was statistically significant ($p<0.001$). There were no severe or clinically significant adverse events during the study follow-up period; neither electrolyte abnormalities nor renal function deterioration was observed. Torasemide was both effective and safe in patients with stage 3b chronic kidney disease and uncontrolled hypertension. This finding supports current recommendations to substitute thiazide and thiazide-like with loop diuretics in patients with advanced renal insufficiency.

Keywords: torasemide, thiazide diuretics, chronic kidney disease, efficacy, safety.

Introduction

Arterial hypertension is a major public health concern, affecting more than 1 billion individuals worldwide [1]. Likewise, chronic kidney disease (CKD) represents another public health issue of major significance since its prevalence is estimated to be between 7 and 15% around the world [2, 3], with a recent 13.1% estimate in the United States [4]. Arterial hypertension and chronic kidney disease are closely interconnected, with chronic kidney disease being both a cause and a consequence of arterial hypertension.

Arterial hypertension is not easily controlled in patients with chronic kidney disease. In the Chronic Renal Insufficiency Cohort (CRIC) study, the majority of patients with renal insufficiency were on three or

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more antihypertensive drugs [5], highlighting the difficulty to attain blood pressure control in these patients.

Thiazides and thiazide-like diuretics are considered first-line options for the management of arterial hypertension [6]. However, they become less effective as renal function deteriorates. According to the current 2018 European Society of Hypertension and Cardiology guidelines: "Both thiazides and thiazide-like agents are less effective antihypertensive agents in patients with a reduced glomerular filtration rate (GFR) [estimated GFR (eGFR) <45 mL/min] and become ineffective when the eGFR is <30 mL/min. In such circumstances, loop diuretics such as furosemide (or torasemide) should replace thiazides and thiazide-like diuretics to achieve an antihypertensive effect" [6].

Loop diuretics represent the cornerstone of heart failure therapy and are widely used in other edematous disorders, such as cirrhosis and chronic kidney disease. Torasemide is a long-acting loop diuretic since its pharmacokinetic and pharmacodynamic properties offer substantial superiority over furosemide; specifically, once-daily dosing as well as high and predictable bioavailability [7].

The aim of our study was to retrospectively evaluate the efficacy of torasemide, a long-acting loop diuretic when replacing thiazides in patients with stage 3b CKD and uncontrolled hypertension.

Material and Methods

This is an observational retrospective study that was designed to evaluate the efficacy and safety of torasemide in patients with uncontrolled hypertension and stage 3b CKD. The current study was conducted at the 2nd Propedeutic Department of Internal Medicine of the Aristotle University of Thessaloniki. The study was approved by the Ethics Committee of the Hippokration Hospital, Thessaloniki, Greece (approval ID: 103/26-5-2021), and all patients have given informed consent that their data can be analyzed at any time, given that their identity is kept confidential, and patients remain anonymized during any stage of data analysis.

For the purpose of the study, the medical records of all patients attending the Hypertension Outpatients Clinic of our Department from January 1st, 2020, until December 31st, 2020, were retrieved and patients with stage 3b CKD were identified. We then isolated the data from patients who were on triple combination antihypertensive therapy with a Renin-angiotensin-system (RAS) inhibitor, a calcium antagonist, and a thiazide diuretic (either as fixed-dose combinations or as separate drugs) and remained uncontrolled. Then, we analyzed the data for patients whose diuretic therapy was switched from thiazides to torasemide.

In summary, patients were included in the analysis if: a) they were >18 years old, b) they were on triple combination antihypertensive therapy with a RAS-inhibitor, a calcium antagonist, and a thiazide or thiazide-like diuretic, c) their blood pressure remained uncontrolled (>140/90 mmHg), d) had stage 3b CKD [estimated glomerular filtration rate (eGFR): 30–44 ml/min/1.73m^2], e) antihypertensive therapy was changed and torasemide replaced a thiazide diuretic, f) written informed consent was granted. Patients were excluded from the analysis if they did not fulfill all inclusion criteria, if they had any other additional changes in hypertension management (either in lifestyle modification or in antihypertensive therapy), or if they had not a follow-up visit at 8–12 weeks after the change of antihypertensive therapy was performed.

Blood pressure was measured at the office according to current guidelines by using an automatic device (M2 Basic HEM 7120, Omron, Japan). eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The categorization of CKD was made according to 5-stage Kidney Disease Outcome Quality Initiative (K/DOPQI) recommendations [8], and stage 3b was defined as eGFR values between 30 and 44 ml/min/1.73m^2. Routine laboratory tests were performed at our Hospital's Central Laboratory using the standard methodology.

The efficacy endpoint was the change in office blood pressure at 8–12 weeks after torasemide initiation, while the safety endpoint included the change in renal function, electrolytes, and the occurrence of any adverse event following torasemide initiation.

Statistical analysis

Data were collected, entered, and then analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0.0. Continuous variables are presented as mean (± standard deviation) or median (interquartile range), according to the existence of normal distribution. Categorical variables are presented as frequencies. The student's t-test was used for the comparison of continuous variables when two values were compared, while the one-way ANOVA test was used when more than two values were compared. For categorical variables, the Chi-Square or Fisher's Exact Test was used for study comparisons according to the number of expected frequencies. A p-value of less than 0.05 was considered statistically significant.

Results

Overall, 403 patients visited our Outpatient Hypertension Clinic with apparent resistant hypertension.

Ambulatory or home blood pressure monitoring revealed that 148 patients had normal blood pressure levels and were thus excluded from the analysis. In addition, 153 patients were not included due to poor adherence to antihypertensive therapy and/or lifestyle modification, drug-induced blood pressure elevation, and secondary hypertension. Furthermore, 78 patients were not fulfilling the specific triple combination therapy at the maximum tolerated doses by the protocol (RAS-inhibitor, calcium antagonist, and thiazide or thiazide-like diuretic). Therefore, 24 patients were eligible for the analysis. The mean age of the study participants was 67.1 years (standard deviation: 6.1 years), they were all of Caucasian origin, and 11 of them were females while the remaining 13 were males. A history of diabetes was present in 8 patients, while a history of cardiovascular disease was present in 9 patients.

The substitution of the thiazide (or the thiazide-like) diuretic by torasemide resulted in significant blood pressure reduction. Systolic blood pressure was reduced from 154.3±5.6 mmHg to 140.2±6.6 mmHg ($p<0.001$) (Figure 1), and diastolic blood pressure was lowered from 86.8±7.6 mmHg to 79.9±5.7 mmHg ($p<0.001$) (Figure 2). In total, systolic blood pressure control was achieved in 65.4% of the patients, diastolic blood pressure control in 96.2% of the patients, while concomitant systolic and diastolic blood pressure control was achieved in 65.4% of study participants.

There were no significant adverse events during the study follow-up period. No hypotensive or syncopic episodes were observed in study participants. Similarly, there were no episodes of acute kidney injury, while the renal function remained practically unchanged following torasemide administration (p=NS; Figure 3). Likewise, no significant changes were observed in serum electrolytes, while no cases of significant electrolyte abnormalities occurring with torasemide administration. Finally, no significant changes in body weight (Figure 4), glucose and lipid levels were seen during the study follow-up period (data not shown).

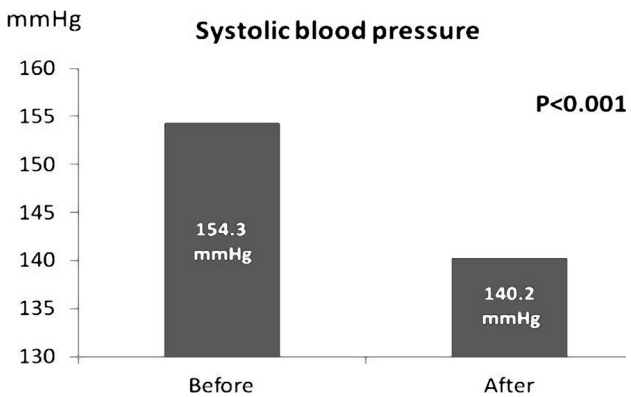

Figure 1. Systolic blood pressure before and after torasemide administration.

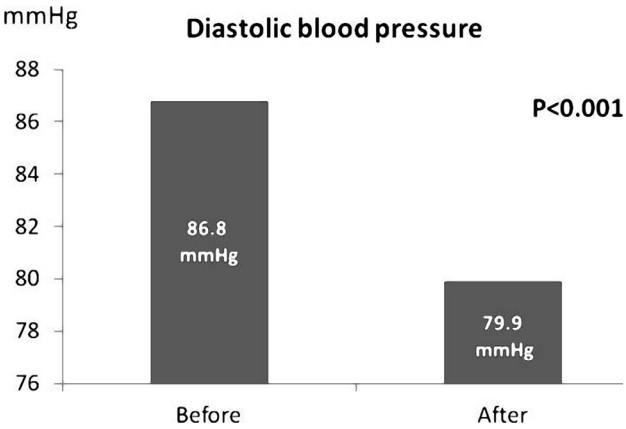

Figure 2. Diastolic blood pressure before and after torasemide administration.

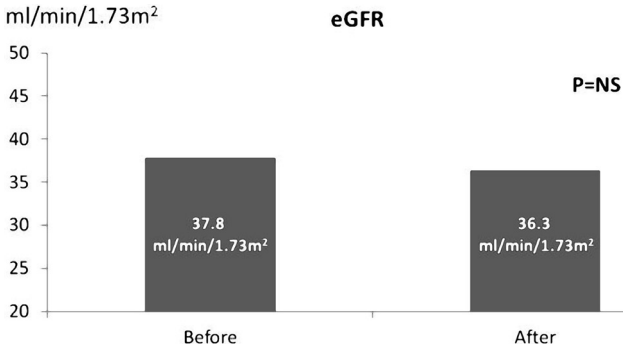

Figure 3. Estimated glomerular filtration rate (eGFR) before and after torasemide administration.

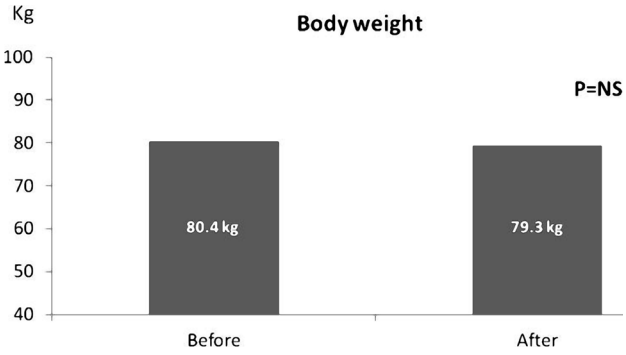

Figure 4. Body weight before and after torasemide administration.

Discussion

In this observational retrospective study, we evaluated the safety and efficacy of replacing thiazides (or thiazide-like) diuretics with torasemide in patients with stage 3b chronic kidney disease and uncontrolled hypertension. Overall, torasemide showed a good safety profile with no significant adverse events, renal function deterioration, or metabolic

and electrolyte abnormalities. Of major clinical significance, torasemide was found very effective in this patient group since its administration was associated with a significant reduction of blood pressure, resulting in blood pressure control in most study participants.

Two studies have been recently performed, and their findings seem to dispute the dogma that thiazide and thiazide-like diuretics are not effective in patients with advanced renal dysfunction.

The first study was a retrospective observational study of 14 patients with advanced chronic kidney disease and an eGFR of 20–45 ml/min/1.73m^2. The study evaluated the effects of chlorthalidone at titrated doses (starting from 25 mg and doubled every 4 weeks if blood pressure remained uncontrolled) for a 12-week follow-up period. It was found that chlorthalidone resulted in significant systolic blood pressure reduction of 10.2, 13.4, and 9.4 mmHg at 4, 8, and 12 weeks, respectively. It has to be noted, however, that all participants were already on torasemide; therefore, this study actually evaluated the effect of chlorthalidone addition to loop diuretics and not the actual effect of thiazide monotherapy. Of major clinical importance, chlorthalidone use was associated with significant adverse events in half of the study participants, including hypokalemia, hyponatremia, hyperuricemia, and renal deterioration [9].

The second recently published study was a 6-week, randomized, open-label study comparing the effects of amiloride/hydrochlorothiazide 5/50 mg with sodium restriction in 26 patients with grade 3 and grade 4 chronic kidney disease. It was found that the study diuretic produced a significant 14 mmHg ambulatory systolic blood pressure reduction, suggesting that distal diuretics maintain their efficacy even in advanced renal dysfunction. However, it has to be noted that the thiazide diuretic was combined with amiloride, a potassium-sparing diuretic, with a different mode of action. Moreover, prior antihypertensive therapy was discontinued for only 2 weeks, therefore not excluding a potential carry-over effect [10].

In contrast, a recent observational study of 312 patients with pre-dialysis chronic kidney disease compared the blood pressure lowering effects of furosemide and hydrochlorothiazide. It was found that furosemide was significantly superior to hydrochlorothiazide, with higher doses of furosemide (80mg thrice daily) resulting in a systolic blood pressure reduction of 10.6 mmHg versus a modest decrease of only 3.7 mmHg with hydrochlorothiazide [11].

Taken together, the findings of the abovementioned recent studies do not permit definite conclusions. It can be argued that there is data supporting the maintenance of thiazide efficacy in advanced kidney disease [9, 10], while other studies, both recent [11] and especially older [12–15], negate the efficacy of thiazide and thiazide-like diuretics in severe renal impairment. It has to be noted, however, that the two positive studies actually used combined diuretic therapy (one with torasemide and the other with amiloride), thus casting doubts about the efficacy of thiazide monotherapy in patients with advanced kidney disease. The findings of our study indirectly support a reduced efficacy of thiazide diuretics in stage 3b chronic kidney disease since the substitution of a thiazide by a loop diuretic was associated with a substantial reduction of blood pressure.

The study is limited by its observational retrospective design, carrying the inherent limitations of retrospective studies. Moreover, the study sample was very small, not permitting definite conclusions. In addition, there is no certainty about the equivalence of diuretic doses since data on this issue is very limited in the literature. Therefore, the findings of our study should be considered only as hypothesis-generating and should be confirmed in large, randomized clinical studies.

Conclusion

Torasemide was found to be safe and very effective when replacing thiazide and thiazide-like diuretics in patients with stage 3b chronic kidney disease and uncontrolled hypertension. Although reports supporting the maintenance of thiazide efficacy in advanced renal insufficiency exist in the literature, the majority of data point towards reduced efficacy, and this is reflected in current guideline recommendations. Our findings indirectly support the latter, suggesting that thiazide and thiazide-like diuretics should be replaced by loop diuretics in patients with stage 3b chronic kidney disease.

Conflict of interest

The author confirms that there are no conflicts of interest.

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