

CLINICAL RESEARCH

The Effects of Torasemide on Patients with Chronic Heart Failure

Bakhrom Alyavi, PhD, ScD¹, Muyassar Mukhamedova¹,
Dina Arnopolskaya, PhD²

¹Republican Specialized Scientific-Practical Medical Center of Therapy and Medical Rehabilitation
²ORION MEDICITY LLC
Tashkent, Uzbekistan

Abstract

This article describes the effects of the additional application of torasemide in 22 patients with chronic heart failure of ischemic origin. It is indicated that torasemide application helps reduce the natriuretic peptide level and improves the central hemodynamics without a significant effect on the blood electrolyte level.

Keywords: Chronic heart failure, natriuretic peptide, torasemide.

Introduction

Chronic heart failure (CHF) is a syndrome that develops because of various cardiovascular diseases that occurs in the presence of systolic and/or diastolic dysfunction accompanied by chronic hyperactivation of the neurohormonal systems. The main reasons responsible for more than half of all heart failure cases are ischemic heart disease (IHD) and hypertension or a combination of these [1].

The development of chronic heart failure is a complex pathophysiological process arising from changes in the pumping function of the heart, volume overload (fluid retention), and neurohumoral activation. Chronic neuroendocrine stimulation causes sodium and water retention, vasoconstriction, exerting toxic effects on the cardiomyocytes [2].

Research objective was to study the effect of the loop diuretic torasemide on central and intracardiac hemodynamics, NUP and electrolyte levels in patients with chronic heart failure of ischemic origin.

Material and Methods

In all, 22 patients (mean age 62.54 ± 4.91) with CHF of ischemic origin were examined. For the control group, 20 healthy volunteers of comparable age, with no symptoms of cardiovascular diseases were examined.

All the patients in the study were diagnosed with CHD: stable exertional angina FC-II (7 patients), FC-III (15 patients); 13 patients had prior history of myocardial infarction.

At the time of admission, all the patients in the study had been receiving basic medication: aspirin 75-100 mg/day, angiotensin-converting enzyme inhibitor (lisinopril) (the dose being titrated according to the hypotensive response), statins (atorvastatin 20 mg/day), beta adenoceptor blocking agents (bisoprolol) (the dose being titrated according to the hypotensive response and heart rate). Based on the prescriptions, nitrates were also used (10 patients [45.5%]). After the initial examination, torasemide at 5-10 mg/day dose was included in the treatment scheme.

Initially and after 10 days into the treatment, all the patients underwent the following examinations: electrocardiography, echocardiography, concentration of blood electrolytes (potassium, magnesium, sodium), identification of natriuretic peptide concentration, and determination of exercise tolerance (indicated by the distance covered during the six-minute walk test [6MWT]).

*Corresponding author: Muyassar Mukhamedova, Republican Specialized Scientific-Practical Medical Center of Therapy and Medical Rehabilitation. 4, Osiyo street, Yunusabad district, 100084, Tashkent, Uzbekistan. Fax/Tel: 998-90-1898300/998-90-9100804. E-mail: muyassar1983@mail.ru

The concentration of brain natriuretic peptide (BNP) was measured based on the concentration of the N-terminal fragment of BNP precursor peptide in heparinized venous blood using the quantitative immunological method. The blood plasma electrolyte level was measured employing the photometric method [3].

End-diastolic dimensions of the left atrium (LA), left ventricle (LV), right ventricle (RV), thickness of left ventricular wall, interventricular septum (IVS) and posterior wall of left ventricle (PWLV) were measured by echocardiography in M-mode with navigation in B-mode in the left parasternal long-axis position, in accordance with the rules of Penn convention method. Measurement of end diastolic and systolic LV volumes (EDV and ESV of LV) was carried out using the modified Simpson's method in the apical 2-wire and 4-chamber view. Then, using the standard formula, stroke volume (SV) and ejection fraction (EF), which characterize LV systolic function, were calculated.

Blood plasma electrolyte level was measured by photometric method.

All the data was processed employing the variation statistical methods using the software Statistica for Windows 6.0. For data with normal distribution, inter-group comparisons were performed using student's t-test. The mean (M) and standard error (SE) of the mean were calculated. The difference was considered reliable when $p < 0.05$.

Results and Discussion

Clinically, CHF in all the patients in the test group was characterized by edema and shortness of breath during physical activity. Whereas 8 (36.4%) patients with CHF were categorized with Functional Class II, the remaining 14 patients were identified as Class III as per NYHA (1964).

The occurrence of heart failure was confirmed by a higher BNP level in the patients under study, compared with the control group of healthy people ($p < 0.001$) (Table 1). The increased secretion of the natriuretic peptides begins in the early stages of CHF. It is one of the earliest compensatory mechanisms that counteracts the sodium and water retention in the body, excessive vasoconstriction and increased pre-and afterload. The activation of the natriuretic factor in CHF is associated with the deterioration of intracardiac hemodynamics, as well as with the increased activity of local and circulating neurohormones [4].

Tolerance to physical exercise was assessed by a 6-minute walk test. The test revealed a significant drop in the distance covered by patients with heart failure compared with the healthy individuals ($p < 0.001$). The main causes for complaints and test discontinuation (observed in 10 patients - 45.5%) were shortness of breath and fatigue. No strokes of angina were detected.

Compared with the reference group, the tension in the mechanisms of neurohumoral regulation, including BNP-mediated tension, was apparent through significantly lowered blood electrolyte concentration ($p < 0.01$ for potassium and magnesium, $p < 0.001$ for sodium), despite basic treatment, although in general, the concentration remained within the normal range. Sodium reduction is caused by the BNP effect [5], while the lowered potassium and magnesium results from the activation of the renin-angiotensin-aldosterone system [6].

From the hemodynamic viewpoint, patients with CHF displayed an overall decreased LV contractility, characterized by

Table 1.

BNP and blood electrolyte concentration and central hemodynamic indicators in patients with ischemic CHF during the 10-day torasemide therapy

Parameters	Healthy participants (n= 20)	At admission (n=22)	After 10-day treatment (n=20)
BNP, pg/ml	65.34 ± 6.45	977.2 ± 102.1 ^{^^^}	850 ± 99.2 ^{***}
Potassium, mmol/L	5.2 ± 0.16	4.1 ± 0.17 ^{^^^}	4.24 ± 0.16
Sodium, mmol/L	142 ± 2.4	147.65 ± 2.3 ^{^^^}	140.2 ± 1.7 ^{**}
Magnesium, mmol/L	0.9 ± 0.02	0.86 ± 0.03 ^{^^}	0.78 ± 0.02 [*]
6MWT	670.09 ± 12.06	294.09 ± 11.08 ^{^^^}	319.09 ± 11.19 [*]
Left atrium, cm	3.6 ± 0.06	4.2 ± 0.07 ^{^^^}	4.11 ± 0.06 [*]
IVS, cm	1.00 ± 0.04	1.17 ± 0.05 ^{^^}	1.1 ± 0.03
PWLV, cm	0.90 ± 0.02	1.08 ± 0.03 [^]	1.05 ± 0.02
RV, cm	2.20 ± 0.03	2.69 ± 0.04 ^{^^}	2.63 ± 0.04
EDD, cm	5.78 ± 0.04	5.78 ± 0.04 ^{^^^}	5.6 ± 0.08
ESD, cm	4.9 ± 0.05	4.25 ± 0.06 ^{^^^}	4.11 ± 0.05 ^{**}
EDV, ml	112.80 ± 3.16	166.4 ± 3.14 ^{^^^}	164.45 ± 3.2
ESV, ml	42.86 ± 2.63	82.8 ± 2.8 ^{^^^}	76.39 ± 2.34 [*]
SV, ml	69.93 ± 1.89	83.54 ± 1.9 ^{^^^}	87.66 ± 1.9
EF, %	62.00 ± 0.82	50.9 ± 0.9 ^{^^^}	53 ± 0.92 ^{**}
Heart rate, bpm	74.23 ± 0.9 3	84 ± 2.3 ^{^^}	76.36 ± 0.87 [*]

Note: significance of difference between CHF and healthy participants is marked [^], significance of difference between initial state and after 10-day torasemide treatment of CHF group is marked ^{*}. One symbol represents $p < 0.05$, two symbols – $p < 0.01$, three symbols – $p < 0.001$.

a lowered left ventricular ejection fraction ($p < 0.001$). However, an increase in the LV diameter and volume ($p < 0.001$) allowed the maintenance of a higher stroke volume compared with the control group, despite a reduced ejection fraction of the heart ($p < 0.001$). The increase in the volumes of the heart chambers (LV, PL - $p < 0.001$, RV - $p < 0.01$) indicates one of the mechanisms of progressive heart failure: fluid and sodium retention due to lower renal perfusion and the activation of the nephrons of the juxtaglomerular apparatus, followed by the tension of the renin-angiotensin-aldosterone system (RAAS) [7]. Reactive sympathetic activation, observed as a response to the tension of the neurohormonal mechanisms of heart failure, increases the heart rate in patients with chronic heart failure ($p < 0.001$ compared to the control group), which was also observed in our study, despite the application of beta-blockers that are part of the basic therapy. Also, CHF patients displayed a significant increase in the left ventricular wall thickness ($p < 0.05$ for PWLV and $p < 0.01$ for IVS), which probably results from calcium resetting, typical to ischemic heart disease, and the response of the myocardial receptors to angiotensin II, which activates the nuclear mechanism of protein synthesis and hyperplasia of the cardiomyocytes [8].

Thus, the initial examination of patients with ischemic heart failure included in the study showed that, despite application of basic therapy, patients suffered tension of the neurohumoral regulatory systems that supersede the compensatory level and play a pathophysiological role. In particular, the study revealed signs of sympathetic-adrenal system and RAAS hyperactivity (increased heart rate, reduction of potassium, magnesium in blood, increased myocardial wall thickness and volume of cardiac cavities), and increased BNP concentration.

After the initial examination, 5 to 10 mg of the loop diuretic torasemide (based on the severity of the edema syndrome) was additionally introduced in the treatment of all the patients in the study, one time in the morning on an empty stomach. Follow-up revealed that the 10-day diuretic torasemide therapy resulted in a significant reduction of peripheral BNP concentration compared with the source data ($p < 0.001$). Loop diuretics most often exert a natriuretic effect, which helps to reduce fluid retention, preload on the myocardium and restrict its over-distension, ultimately decreasing the BNP activity. Lowered fluid retention reduces clinical symptoms, despite slower systolic heart functions. The reduced dyspnea, in particular, increased the distance covered during the 6-minute walk test ($p < 0.05$ of source data). Also, the diuretic torasemide therapy was observed to **lower the** heart rate in CHF patients without increasing the beta-blocker dosage ($p < 0.05$), which in turn probably results from the drop in the activity of the sympathetic-adrenal system caused by decreased fluid retention. Clinically, 5 patients moved from heart failure Functional Class III to Class II per NYHA clinical classification with a total of 13 (59.1%) patients having FC II (frequency difference in the distribution of CHF patients FC is insignificant).

The diastolic volume of the left atrium ($p < 0.05$) and left ventricle decreased, which, with the LV systolic function being constant, led to a decreased stroke volume (insignificant); however, it remained higher than in the group of healthy participants.

When utilizing loop diuretics, one should recognize their ability to disrupt the blood electrolyte composition. This study demonstrated that during the 10-day treatment with torasemide combined with ACE inhibitor lisinopril, the initially low blood magnesium concentration decreased ($p < 0.05$), while the potassium concentration remained unchanged. The sodium concentration dropped ($p < 0.01$ from baseline), although it stayed within normal range. T. Bolke and I. Achhammer, in their studies, also established that torasemide exerted a minimal effect on the serum potassium, sodium and magnesium levels, which remained stable even after prolonged use of the drug, in 5-20 mg doses, in CHF patients [9].

Despite the changes in the electrolyte status, none of the patients in the study showed either the occurrence or progression of dangerous arrhythmias.

Conclusions

Despite the basic therapy, CHF patients were found to retain over-tension of the initial compensatory neurohormonal mechanisms of heart failure, which develop into the pathophysiological phase of HF progression; The inclusion of loop diuretic torasemide into the 10-day basic therapy of CHF reduces systemic sympathoadrenal activity, sodium and fluid

retention, as well as lowers the clinical CHF FC minimally impacting the potassium and magnesium concentration.

References

1. Makolkin V. Features of the modern treatment of chronic heart failure. <http://medinfo.ru/article/7/118619/>. [in Russian].
2. Karpov YuA. Angiotensin-receptor blockers: use in heart failure. *RMJ* 2002; 2:51-54. [in Russian].
3. Arakawa N, Nakamura M, Aoki H, Hiramori K. Plasma brain natriuretic peptide concentrations predict survival after acute MI. *J Am Coll Cardiol* 1996; 27(7):1656-61.
4. Dobrek Ł, Thor P. Neuroendocrine activation as a target of modern chronic heart failure pharmacotherapy. *Acta Pol Pharm* 2011; 68(3): 307-16.
5. Packer M. Do angiotensin-converting enzyme inhibitors prolong life in patients with heart failure treated in clinical practice? *J Am Coll Cardiol* 1996; 28(5):1323-7.
6. Staessen J, Lijnen P, Fagard R, Verschueren LJ, Amery A. Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. *J Endocrinol* 1981; 91(3):457-465.
7. Ovchinnikov A. Recent advances in the diagnosis of heart failure by the level of natriuretic peptide. *Heart failure* 2003; 4(3):158-160.
8. Apple FS, Panteghini M, Ravkilde J, Mair J, Wu AH, Tate J, et al. Committee on standardization of makers of cardiac damage of the IFCC. Quality specifications for B-type natriuretic peptide assays. *Clin Chem* 2005; 51:486-493.
9. Bolke T, Achhammer I. Torasemide: review of its pharmacology and therapeutic use. *Drugs of today* 1994; 8: 1-28.