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Safety of chronic heart failure complex therapy: results of randomized crossover study BASTion

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Summary:

Objective

To estimate the safety of complex therapy of patients with chronic heart failure after adding to treatment diuretics with different influence on potassium excretion.

Matherials and methods

19 patients over 18 years with stable chronic heart failure (CHF), II and III NYHA class, were included in randomized crossover study. All patients were administered with standard CHF therapy: β-blocker, angiotensin-converting enzyme (ACE) inhibitor, mineral-corticoid receptor inhibitor and diuretic. Patients' therapy did not change until one month before randomization. After randomization patients were subdivided into two groups: first group (8 persons) started diurethic therapy with furosemide, second one (11 persons) started diuretic therapy with torasemide. Therapy was estimated after one month and patients who took torasemide started to take furosemide fore one more month and vice versa, patients who previously received furasemide changed it to torasemide. All patients received medicines in necessary doses according with their clinical condition.

Results

Average age of patients included in the study was 68,2±9,5 years. 52,6% of patients were males. Average dose of torasemide in the study was 24,5±7,4 mg per week, and average dose of furosemide was 111,6±16,8 mg per week. Used average doses of four-component therapy did not lead to occurrence of hyperkaliemic conditions. Results of 6-minute walk tests revealed improved tolerability of physical exercise after torasemide treatment. Torasemide was better tolerated by patients.

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Conclusion

Lack of reflex tachycardia in response to torasemide therapy allows to recommend it for the majority of patients with CHF especially to the ones with comorbid pathologies.

Keywords

Torasemide, chronic heart failure, hyperkalemia, hypokalemia, 6-minute walk test

Introduction

It is necessary to use obligatory drugs like ACE inhibitors/sartans, beta-blockers, mineralocorticoid receptor antagonists (MCRA) for the treatment of people with chronic heart failure. It is known that ACE inhibitors and MCRA can lead to body retention of the potassium [1, 2]. Awareness of hyperkalemia development in patients is growing due to the fact that the majority of patients is older than 60 years and they can have impaired kidney function. Nevertheless, the results of R. Pisoni [3] demonstrate that hyperkalemia does not develop frequently in patients with chronic kidney disease receiving spironolacton.

The results of the RALES (Randomized Aldactone Evaluation Study) [4] study demonstrate that spironolacton addition to the therapy had advantages over the therapy without spironolacton in patients with heart failure and reduced glomerular filtration rate.

It is necessary to notice that hipokalemia is more frequent that hyperkalemia. For example, G. C. Liamus and colleagues [12] demonstrated that hypokalemia development was 13,5 times more frequent than hyperkalemia.

Often diuretics like torasemide or furosemide are necessary for the treatment of patients with heart failure. Simultaneous treatment with ACE inhibitors/sartans, MCRA and torasemide can cause apprehension of doctors ddue to possible development of hypokalemic conditions.

The objective of our study was to estimate the safety of complex therapy of patients with chronic heart failure after addition of diuretics differently influencing potassium excretion to the treatment.

Materials and methods

19 patients older than 18 years with stable chronic heart failure, NYHA functional classes II or III, were included in open randomized crossover study. All patients received standard chronic heart failure therapy (CHF): beta-blocker, ACE inhibitor, MCRA and diuretic. Patients received this treatment without changes during at least one month before randomization. After randomization patients were splitted into 2 groups: the first group (8 patients) started diuretic therapy from furosemide and the second one (11 persons) started from torasemide. All patients received the drugs in the doses according with their clinical condition.

Exclusion criteria were: clinically significant diseases of liver and kidney (plasma creatinine levels more 221 mmol/L and/or alanine and/or aspartate aminotransferase levels elevation), initial plasma levels of potassium more than 5 mmol/L or less than 3,5 mmol/L, initial plasma levels of sodium less 135 mmol/L. All patients signed informed consent.

Blood samples were taken in the morning on an empty stomach in the beginning of the study and at the end of each period of the study. Each therapeutic period lasted for 4 weeks without washing period between the periods when patients changed drugs.

Changes of potassium and sodium plasma levels were considered as the primary endpoint of the study. Changes of 6-minute walk test results comparing with the initial ones were taken as the secondary endpoint.

To estimate patient's treatment perception we used visual analogue scale (VAS) of general state. In this scale 0 is considered as a "good general state" and 10 as "very bad general state, it can't be worse". Each patient was asked to estimate his general state according with this 10-points scale. Rate between 6 and 10 points was interpreted as a bad general state. This estimation was made after patient's inclusion into the study and after each stage of the study.

To evaluate patient's satisfaction with diuretic therapy we used VAS. In this scale 0 is considered is "absolutely satisfied" and 10 – as "absolutely unsatisfied". So the less was the rate that patient mentioned the more he was satisfied with diuretic therapy. Estimation was performed according with 10-points scale. Rate between 6 and 10 points was considered as low satisfaction with diuretic therapy. Estimation was performed after patient's inclusion into the study and after each stage of the study.

Statistical methods

Computer analysis of the results was performed with SAS software (Statistical Analysis System,

SAS Institute Inc., USA) using parametric and non-parametric algorithms of variance statistics that take into account scales of each characteristic.

For characteristics measured with interval scale we quantified mean value, standard deviation, error of mean, median, interquartile distance, etc. For characteristics measured with nominal scale ("presence/absence') or rank scale we determined the frequency of registration of different ordinal rates of characteristics in percentage.

for analysis of differences between groups measured with interval scale we performed Student's t-test for independent samples according with suitable formulas in three different modifications taking into account the details of statistical distribution of studied characteristics. Significance of intragroup dynamics of these characteristics during the period of treatment was estimated with appropriate criteria for paired measurements.

In case of "binary" characteristics the significance of difference between frequencies of some factor's detection in two compared groups of patients we estimated also using t-test but with arcsin-modification of Fisher.

Paired correlation connections were estimated with linear Pearson's correlation and Spearman's rank correlation coefficients and Tau-b-Kendall's coupling coefficient and Kramer's contingency coefficient, statistical significance of which was estimated with SAS software using appropriate formulas.

Multiple connections between characteristics were modeled using stepped multivariate regression equations, both linear and logistical ones.

Connection between rank and binary characteristics were estimated with contingency tables, and significance of these connections was evaluated by three different modifications of Pearson's x-squared criterion and Fisher's exact test.

Results

Average age of patients included in the study was 68,2±6,5 years. 52,6% of patients were males. Average dose of torasemide in the study was 24,5±7,4 mg/week and furosemide average dose was 111,6±16,8 mg/week.

After furosemide administration sodium plasma levels significantly decreased from 138,42±10,43 mmol/L to 133,21±10,43 mmol/L, so its concentration decreased by 5,21±9,32 mmol/L (p<0,05). Whereas torasemide administration reduced sodium plasma levels from 139,21±2,64 to 136,21±5,46 mmol/L, so they decreased by 3,00±4,73 mmol/L (p<0,05). There were no statistically significant differences between sodium plasma concentrations in patients who took torasemide and furosemide. At the same time patients who were administered with furosemide has reached sodium plasma levels beyond normal concentration of 135 mmol/L.

Table 1. **Initial characteristics of patients**

Characteristic	Value
Number of patients	19
Gender, number of patients: m f	10 9
Age, years	68,3±9,6
Body mass, kg	84,1±13,0
Body mass index	29,5±4,6
History of diabetes, number of patients	10
History of myocardial infarction	9

Table 2. **Initial characteristics of patients in groups receiving different treatment**

Characteristic	"Torasemide" group	"Furosemide" group
Number of patients	11	8
Gender, number of patients: m f	6 5	4 4
Age, years	67,4±9,0	69,5±10,8
Sodium levels, mmol/L,	139,21±2,64	138,42±2,41
Potassium levels, mmol/L	4,43±0,50	4,51±0,44
6-minute walk test, m	261,1±49,3	290,8±43,4*

* p<0,01 in comparison of torasemide and furosemide groups.

During furosemide treatment potassium plasma levels decreased from 4,51±0,44 mmol/L to 4,43±0,45 mmol/L, so its concentration decreased by 0,08±0,49 mmol/L. Torasemide administration resulted in potassium plasma levels increase from 4,43±0,50 mmol/L to 4,51±0,43 mmol/L, so its concentration increased by 0,08±0,33 mmol/L.

Glomerular filtration rate quantified using MDRD formula changed from 75,6±15,2 to 79,9±17,1 mL/min in patients who received torasemide, so it increased by 4,3±11,2 mL/min. Glomerular filtration rate in patients who were taking furosemide changed from 75,9±15,2 to 80,2±17,1 mL/min, so it increased by 4,3±11,2 mL/min.

Results of 6-minutes walk test demonstrated that patients who received torasemide increased the distance of walk by 35,6±24,9 m (13,6%, p<0,001). Patients who took furosemide decreased their distance by 3,1±31,0 m (1,1%).

There was no significant difference in number of patients who passed the distance more than 300m before the beginning of study. But the number of patients who walked more than 300m in the group who received torasemide increased significantly,

and it was not detected in the group of patients who received furosemide.

One important aspect of therapy is its perception by patient. Torasemide treatment resulted in significant improvement of patients' general state by 21,4% (p<0,001), and furosemide treatment has not led to its significant change. More than that, there was a tendency to the worsening of general state by 11,3% in the group of patients who received furosemide.

General state estimated by patient with the rate of 6 and higher was interpreted as bad general state. After torasemide treatment the number of patients with bad general state lowered from 36,8% to 5.3% (p<0,01). furosemide treatment results were opposite: the number of patients with bad general state increased from 15,8% to 36,8%. Before the start of the therapy there was no significant difference between the number of patients with bad general state. Estimation of results after therapy revealed that number of patients with bad general state between the ones who received torasemide was significantly lower (p<0,01).

Changes of patient's satisfaction with diuretic therapy coincided with patients' general state dynamic. Torasemide administration resulted in significant increase of patient's satisfaction with diuretic therapy by 29,6% (p<0,01). There were no significant changes in it after furosemide treatment. More than that, there was a tendency of the lowering of patient's satisfaction with diuretic therapy by 15,1%.

Rate of 6 points and higher was considered as low satisfaction with diuretic therapy. After torasemide treatment the number of patients with lowered satisfaction with therapy decreased from 31,6% to 10,5% (p<0,05). There were no changes of patient's satisfaction with diuretic therapy after furosemide administration.

In our study we estimated the influence of therapy on different clinical characteristics. So, systolic blood pressure (SBP) has lowered by 7,4±6,9 mm Hg. (5,5%, p<0,001) after torasemide treatment. After furosemide treatment SBP has lowered by 2,6±9,9 mm Hg. (2,0%). Diastolic blood pressure (DBP) has decreased by 5,4±6,6 mm Hg. after torasemide treatment. (6,8%, p<0,01). DBP has decreased by 0,2±9,0 mm Hg. (0,3%) after furosemide treatment.

It is interesting to notice the fact that the heart rate (HR) during torasemide treatment has lowered by 3,7±4,5 beats per minute (5,3%, p<0,01). During furosemide treatment HR has increased by 4,3±4,9 beats per minute (6,3%, p<0,01). There was no difference between HR of two groups of patients before treatment. After the end of the therapy the difference between HR in two groups was 6,7±3,5 beats per minute (p<0,001).

Discussion

The results of our work did not reveal hyperkalemic conditions. Thus, short-term treatment around 2 months from the start of CHF treatment is unlikely to result in development of hyperkalemia. But one recent study revealed the development of hyperkalemic condition in clinical practice with the incidence of 0,92-7,93 episodes for each 100 person-years [8]. It is necessary to take into account that the average age of patients in this study was 75 years. The highest frequency of hyperkalemia was present in elderly patients with diabetes mellitus and kidney diseases. Average age of patients in our study was less.

Another recently finished study [9] revealed 4.3% of hyperkalemic events in patients receiving contemporary CHF therapy.

Thus the risks of hyperkalemia development are possible. Because of this it is necessary to control potassium plasma levels before the start of therapy, and 1 and 3 months after the beginning of CHF therapy.

Addition of diuretics to the complex therapy of patients with CHF aims to stabilize the balance of water and salts. Prevention of exacerbations and admission to hospital depends mostly on the stability of this parameter.

Our results demonstrate the reduction of sodium plasma levels lower than 135 mmol/L during furosemide treatment that can be considered as an unfavorable factor. Taking into account the fact that torasemide did not lead to the decrease of sodium plasma concentration, it can be considered as an advantage of torasemide over furosemide in outpatients with CHF.

Dynamics of potassium plasma levels during furosemide an torasemide treatment had different directions: its increase by 0,08 mmol/L for furosemide and its decrease by 0,08 mmol/L for torasemide. In both cases these changes were insignificant. Cosin J. and coauthors [10] demonstrated that the necessity of hypokalemic conditions correction was significantly less during torasemide therapy comparing with furosemide.

Taking into account all above-mentioned factors, furosemide therapy in outpatients requires additional control of blood electrolytes, that not only creates additional burden for doctors and hospitals but brings also economical problems for healthcare system in general.

Electrolyte abnormalities can lead to impaired cardiac rhythm. The work of Shugushev [11] demonstrated that patients with CHF who took

torasemide had less ventricular heart rhythm abnormalities comparing with patients receiving furosemide. Probably it is related to lower potassium excretion from human organism during torasemide treatment comparing with furosemide.

Glomerular filtration rate increase during the treatment with both diuretics can be considered as a good tendency.

Significant increase of 6-minute walk distance was detected only in patients who received torasemide. These data go along with the results of V.Yu. Mareev [5] study in hospital patients with CHF and the TRIOLYA study of professor F.T.Ageev in outpatients [6].

More significant decrease of SBP and DBP during torasemide treatment allows to think about torasemide prescription to the patients who require more strict control of BP, for example it can be recommended to the patients with concomitant diabetes mellitus.

Heart rate reduction during complex therapy including torasemide as a diuretic demonstrates lack of sympathetic nervous system activation. It was also proved in the study of K. Harada [7]. Thus it can be considered as an additional advantage of torasemide inclusion into complex therapeutic algorithms of comorbid patients.

Conclusion

Four-component therapy of patients with chronic heart failure, NYHA functional classes II or III, consisted of beta-blocker, ACE inhibitor, spironolactone in 25 mg dose and diuretic did not cause significant increase of potassium plasma levels. Hyperkalemic conditions have not been registered.

The results of 6-minute walk test have significantly improved after torasemide treatment and have not changed after furosemide administration. Torasemide was better tolerated by patients.

Lack of reflex tachycardia development during torasemide therapy allows to recommend it to the majority of CHF patients, particularly to the ones with comorbid pathologies.

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