

SEVERE HYPERKALEMIA: A RETROSPECTIVE ANALYSIS

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Aim: Nowadays, combination of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) with spironolactone is used to treat patients with heart failure or hypertension. Unfortunately these drugs may lead to increase in morbidity and mortality dependent on severe hyperkalemia. We aimed to evaluate the therapeutics and demographic features of patients with hyperkalemia.

Methods: 39 patients with hyperkalemia were evaluated retrospectively whom hospitalized with various diagnoses.

Results: Mean age and serum potassium level were (20 female and 19 male) 68.3±10.2 years and 6.8±0.7 mmol/L at admission. Twenty one patients (53.8%) used ACEI, ARB or spironolactone. The patients were divided into three groups according to their medications: patients that use anyone of the ACEI, ARB or spironolactone, patients that use combinations of these drugs and patients that do not use these drugs. The prevalence of age and diabetes were significantly high in group I and II (p=0.020 and p=0.034 respectively).

Conclusion: In our study mean age and rate of the diabetics were high in group that use ACEI, ARB or spironolactone attract our attention. Therefore, patients should be carefully evaluated about older age and diabetes during prescription of these drugs (alone or in combination).

Key words: Hyperkalemia, spironolactone, ACEI, ARB

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INTRODUCTION

Angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) are commonly used in clinical practice to treat hypertension and decrease cardiovascular events in high-risk patients (1). Clinical trials have shown that the addition of spironolactone to ACEI therapy results in clinical improvement among these patients (2,3) and has beneficial effects on left ventricular hypertrophy in essential hypertension (4).

Randomized Aldactone Evaluation Study (RALES) demonstrated that treatment with spironolactone substantially reduced morbidity and mortality in patients with severe heart failure. After this study, spironolactone, as well as ACEI, has been essential in the treatment of heart failure (5). The most common side effect of ACEI and spironolactone combination therapy is hyperkalemia. Medication-induced hyperkalemia is common, and often life threatening. Hyperkalemia may develop

related with many drugs in patients with underlying renal impairment or other abnormalities in potassium handling (6). Eventually, in patients with hypertension and/or heart failure, mortality and morbidity from hyperkalemia may increase as a result of combined treatment with ACEI, ARB and spironolactone.

The aim of the study is to evaluate the therapeutic and demographic features of patients with hyperkalemia who were hospitalized for any medical reason.

MATERIAL AND METHODS

The study was conducted at Afyon Kocatepe University Hospital, Afyonkarahisar, Turkey. From June 2004 to February 2005, we identified 39 consecutive patients with serious hyperkalemia (defined as serum potassium level >6 mmol/L) who were admitted to the University Hospital for various medical reasons. General data including age, sex, drugs (digoxin, nonsteroidal anti-

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Table 1. Demographic and clinical characteristics of groups*

Variables	Single drug group (n=9)	Combination group (n=12)	No drugs group (n=18)	Total (n=39)	p
Age (mean, year)	74.3±6.2	70.7±9.7	63.7±10.3	68.3±10.2	0.020
Gender (female:male) [‡]	4:5	7:5	9:9	20:19	0.811
Potassium (mmol/L)	6.8±0.9	7.1±0.7	6.6±0.6	6.8±0.7	0.260
Creatinine (mg/dl) [†]	4.0±2.7	2.7±2.3	5.1±4.7	4.1±3.8	0.118
Creatinine Clearance	22.1±16.3	37.6±24.0	22.6±20.5	27.1±21.4	0.127
Diabetes (count, %) [‡]	6 (66.7)	5 (41.7)	3 (16.7)	14 (35.9)	0.034
Requirement of HD (count, %)	1 (11.1)	6 (50)	5 (27.8)	12 (30.8)	0.150
Hospitalization (day) [†]	11.3±7.5	21.9±20.5	6.7±4.8	12.4±13.7	0.176

* All parameters expressed as mean ± SD and compared by One-Way ANOVA unless otherwise stated.

[†] Expressed as median (range) and compared by Kruskal Wallis test, [‡] Comparison by Chi-square test.

inflammatory drugs, beta-blockers, thiazide diuretics, and insulin), serum potassium, creatinine, creatinine clearance and ECG were recorded from hospital files. Creatinine clearance was calculated according to the MDRD. The patients were divided into three groups according to their hyperkalemia reasons: 1) hyperkalemia due to ACEI or ARB; 2) due to any combination of ACEI and/or ARB and/or spironolactone; 3) free of ACEI, ARB or spironolactone.

All clinical parameters were summarized by descriptive statistics. Categorical parameters were compared by Chi-square test. Comparisons of continuous parameters between groups were made by One-Way ANOVA and Kruskal Wallis tests. If distributions of the continuous samples not normal Mann-Whitney U test was used. P values of less than 0.05 were considered to indicate significance. Statistical analysis was performed by SPSS for Windows software (Version 10.0).

RESULTS

The mean age of 39 patients (20 female, 19 males) was 68.3±10.2 year. Demographic and clinical characteristics of patients are shown in Table 1. At the time of admission, mean serum potassium and creatinine clearance were 6.8±0.7 mmol/L and 27.1±21.4 ml/min per 1.73 m², respectively. Twelve patients (30.8%) needed at least one hemodialysis session, and 1 patient needed 5 sessions until renal functions recovered. Six patients died during follow-up. The main

cause of mortality in one patient was hyperkalemia.

Nine patients were using ACEI or ARB, 12 patients were using ACEI and/or ARB and/or spironolactone. Eighteen patients were not using these drugs. Totally 21 (53.8%) patients were using one of these drugs. Eleven patients were using combination included spironolactone and the mean daily dose of spironolactone was 52.2±37.8 mg. Only 4 patients (35.9%) of 14 diabetics were using insulin. Several patients treated with medications that may alter serum potassium level, such as beta-blockers (n=5), digoxin (n=5) and non-steroidal anti-inflammatory drugs (n=3), furosemide (n=2), hydrochlorothiazide (n=5).

In comparison of these groups the mean age and the rate of the diabetics were significantly low in third group (p=0.020 and p=0.034 respectively) (Table 1).

Results of the bipartite comparisons: There was no significant difference between group 1 and 2. In group 3, there was significantly low diabetes prevalence and mean age than group 3 (p; 0.020 and p; 0.034 respectively) (Table 1).

DISCUSSION

In patients with congestive heart failure, the renin-angiotensin-aldosterone system is markedly activated. Excessive systemic and probably also local aldosterone production promotes induction of hypertrophy and fibrosis of the heart muscle. Excessive neurohumoral activation could have been reduced by ACEI, ARB or spironolactone. Because

these drugs reduce the fibrosis with neurohumoral suppression, they frequently have been used to treat heart failure or hypertension with combination or single (7,8). But combination therapy increases the risk of hyperkalemia.

Incidence of serious hyperkalemia was only 2% in the spironolactone treatment group in the RALES trial (5). In other studies, it was reported that these treatments responsible for 10 to 38 per cent of the cases of hyperkalemia (8,9). Particularly older age, renal insufficiency or diabetes mellitus or taking ACEI, ARB and /or spironolactone are independent risk factors for hyperkalemia in patients with heart failure (10,11). Cruz et al. reported that the risk of hyperkalemia due to ACEI or ARB may be increased by the concomitant use of spironolactone (12).

In the other hand, Svensson et al. reported that concomitant use of spironolactone with ACEI or ARB doesn't increase the risk of hyperkalemia (13). The taking rate of ACEI, ARB and /or spironolactone in our study was 53.8 per cent. Besides these risk factors for the development of higher serum potassium levels, the dosage of spironolactone may also be important. While the recommended dose of spironolactone is 25 mg, in our study the mean daily dose of spironolactone was 52.2 mg (14).

In the present retrospective study, the serum creatinine levels were high in most of the patients, and were not significantly different among groups. This observation suggested that impaired renal function is the major cause of hyperkalemia.

In conclusion, the use of ACEI, ARB, or spironolactone alone or in combination with each other is common among diabetics and elderly patients. Therefore, serum potassium levels should be monitored closely during therapy with ACEI, ARB, or spironolactone, especially in patients with older age, diabetes and renal failure, to prevent hyperkalemia.

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