Evaluation of Rise in Creatinine in Concomitant Use of Angiotensin Receptor Blockers and Mineralocortioid Receptor Antagonist

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KEYWORDS

A B S T R A C T

Cardiovascular diseases are common and costly medical condition. Nowadays, combination of angiotensin receptor blockers (ARB) with aldosterone receptor blocker is used to treat patients with heart failure or hypertension. Angiotensin II receptor blockers (ARBs) are an alternative for patients who cannot tolerate angiotensin converting enzyme inhibitors because of their cost and side effects (e.g., cough). Unfortunately these drugs may lead to increase in morbidity and mortality dependent on severe hyperkalemia. The review aims to evaluate the therapeutics and demographic features of patients with hyperkalemia. These cases revealed, close monitoring of blood chemistry is mandatory after starting spironolactone.CHF patients taking angiotensin receptor blocker and spironolactone were taken and their effect of serum potassium were considered.

Introduction

Cardiovascular disease (CVD) is a general term that describes a disease of the heart or blood vessels. Blood flow to the heart, brain or body can be reduced as the result of a blood clot (thrombosis), or by a build-up of fatty deposits inside an artery that cause the artery to harden and narrow (atherosclerosis). Conditions that involve narrowed and blocked blood vessels is generally referred as cardiovascular diseases.

Heart failure is a progressive disorder that begins with myocardial injury. In response to the injury, a number of compensatory responses are activated in an attempt to maintain adequate cardiac output, including the sympathetic nervous system, increased

preload, vasoconstriction, and ventricular hypertrophy/remodeling. These compensatory mechanisms are responsible for the symptoms of heart failure and contribute to disease progression.

Coronary artery disease is the most common type of heart disease. It happens when arteries that supply blood to heart muscle become hardened and narrowed. This is due to the buildup of cholesterol and other materials, called plaques on their inner walls. Overtime, CAD can also weaken heart muscle and contribute to heart failure.

Activation of endogenous neurohormones, including norepinephrine, angiotensin II, aldosterone, vasopressin, and numerous proinflammatory cytokines, play an important role in ventricular remodeling and the subsequent progression of heart failure. Importantly, pharmacotherapy targeted at antagonizing this neurohormonal activation has slowed the progression of heart failure and improved survival.

Nowadays, combination of angiotensin converting enzyme inhibitor, angiotensin receptor blocker with spironolactone is used to treat patients heart failure or hypertension. Unfortunately these drugs may lead to increase in morbidity and mortality on severe hyperkalemia.

In the presence of neurohormonal activation, angiotensin II causes aldosterone production in the adrenal cortex, which acts on the cortical collecting tubules to conserve sodium. Aldosterone may induce perivascular and interstitial cardiac fibrosis that may reduce systolic function, increase cardiac stiffness, and thereby impair diastolic function, generating heterogeneous intracardiac conduction defects with potential for serious re-entrant arrhythmias. Aldosterone may also increase vulnerability to serious arrhythmias by inhibiting cardiac

noradrenaline reuptake, impairing baroreflex-mediated heart rate variability, augmenting sympathetic activity, inhibiting parasympathetic flow, and impairing arterial compliance. Aldosterone also promotes potassium and magnesium depletion, which is potentially proarrhythmic.

Angiotensin receptor antagonist block the activation of angiotensin II receptors. Blockage of the receptor directly causes vasodialation, reduces the secreation of vasopressin and reduces the production and secretion of aldosterone, among other actions.

By competing with aldosterone for receptor sites in distal renal tubules, spironolactone increases sodium chloride and water excretion while conserving potassium and hydrogen ions. The inhibition of sodium reabsorption leads to reduced potassium excretion. Potassium-sparing diuretics have a relatively weak natriuretic effect.

Creatinine is the breakdown product of muscle metabolism. Higher level of creatinine indicate lower glomerular filteration rate and may lead to CKD. Hyperkalemia is an another common clinical condition that can be defined as a serum potassium concentration exceeding 5.0 mmol/L.

Drug-induced hyperkalemia may be asymptomatic. However, it may be dramatic and life threatening, posing diagnostic and management problems. A wide range of drugs can cause rise in creatinine and hyperkalemia by a variety of mechanisms. Drugs can interfere with potassium homoeostasis either by promoting transcellular potassium shift or by impairing renal potassium excretion. The reduction in renal potassium excretion due to inhibition of the renin-angiotensin-aldosterone system represents the most important mechanism by

which drugs are known to cause hyperkalemia. Potassium-containing agents represent a group of medications causing hyperkalemia. Increased awareness of drugs that can reduce these conditions, and monitoring and prevention are key elements for reducing the number of hospital admissions, morbidity and mortality.

Adherence to cardiovascular medications is often suboptimal, and nonadherence is associated with adverse health outcomes as well as increased healthcare expenditure. The goal of this study was to assess the usefulness of the Morisky scale for identifying patients who are nonadherent with cardiovascular medications.

Methodology

A prospective experimental study was carried out to investigate the prevalence of rise in creatinine and potassium on concomitant use of spironolactone and angiotensin receptor blockers in a population of the Pushpagiri Medical College Hospital after receiving approval from our local institutional review board. 56 patients were involved in the study out of which 28 patients receiving spironolactone alone referred as control and other 28 were receiving spironolactone and ARB named as test.

Information was collected on various demographic, comorbid, and laboratory variables including age, body mass index (BMI), classified heart failure (CHF), diabetes mellitus (DM), arterial hypertension (HTN), cholesterol, serum sodium, potassium, serum creatinine (Cr) Glomerular fileration rate (GFR), from the case records and discussions conducted with the patients and bystanders during the ward rounds with the support of a physician on data collection form. Information was also collected on medication usage: ARB type and dose, combination of ARB and spironolactone. CKD patients and patients that take drugs that induce hyperkalemia were excluded from the study.

Morisky Medication Adherence Scale (MMAS-4)

Morisky Medication Adherance Scale was used to determine medication adherence. Each 'yes' answer is given 1 mark. Higher scores shows low adherence.

A case control study of heart failure patients treated with potassium sparing diuretics and angiotensin receptor blocker is conducted in our clinical practice.

Determination of serum creatinine

Using semiautomatic analyser, serum creatinine over a month period was reviewed, the highest value identified, and concurrent laboratory values recorded. Residual blood was collected in a vial by asceptic condition. Serum creatinine was determined by Kinetic method by mixing 250μl R1, 250 μl R2 and 50 μl sample.

Determination of GFR

After obtaining patients age and MyoQuadratic equation was used to deternmine GFR in these patients.

Cases where patients who developed renal insufficiency (Cr>2.5mg/dl) or hyperkalemia. a (K>5 mEq/L) and GFR were compared to randomly selected case control per case. Clinical characteristics, medication and serum chemistries at baseline is compared. Results were generated using standard statistical software. A p-value less than 0.05 was considered significant.

Results and Discussion

The background of 56 patients enrolled in the study, the mean age was 67 ± 12 years. Males occupied 62% of the patients, and 38% female. Weakness, dizziness, shortness of breath, irregular heart beat and chest pain were their initial symptoms. Pearson Chi-square test was used to determine demographic details. Patients were classified according to Body Mass Index(BMI) as 12 Healthy, 14Obese and 30 overweight. Obese patients were more prone to increased creatinine levels with p-value 0.734. There were no significant differences between the two groups with regard to age, gender, BMI, diabetes mellitus, or hypertension. Out of 28 ARB users, 63.6% were on Losar, 56%Valsar, 54.9% Valent, 54.9% Cresar, 53.8% Olmesar. However by Continuity Correlation Method, Losar and Valsar was found to be significant with p-value=0.001 and 0.03respectively. 51patients were highly adherent. Among them, 27 were using spironolactone alone and 24 were using the combination with p-value of 0.352.

Potassium was found to be increased significantly with p-value of 0.001 with in the control group and 0.02 with patients with spironolactone and ARB. However creatinine was significant at p=0.001 and p=0.069 respectively. The mean value of potassium was 4.7 ± 0.5 and creatinine 1.41 ± 0.3. On the other hand, Sodium levels were significantly decreased (p-value=0.001) with mean value of 130 ± 4. A negative impact was visualised in the Glomerular Filteration Rate (GFR).GFR decreases significantly at 0.001 for patients with spironolactone and 0.031 with both spironolactone and Angiotensin Receptor Blocker with mean value of 60 ± 20. Greenhouse-Geisser was used to determine biochemical changes. Creatinine was positively correlated, while GFR was negatively correlated with hyperkalemia.

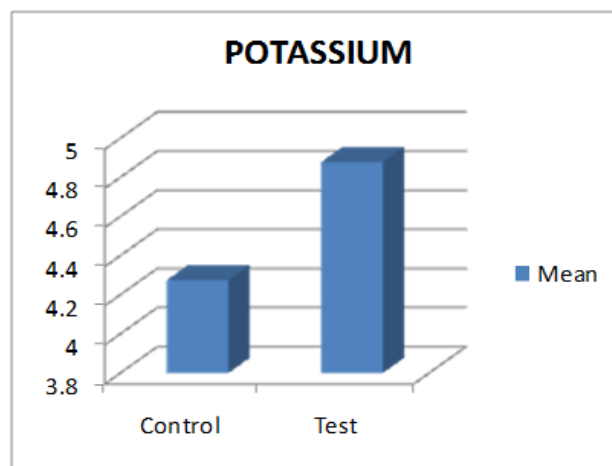**Fig.1** Potassium levels of spironolactone and spironolactone with ARB

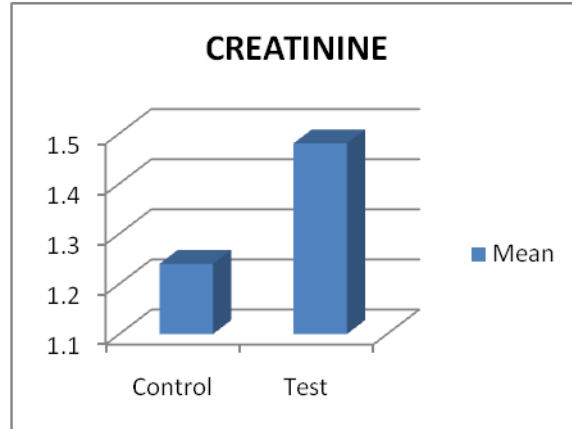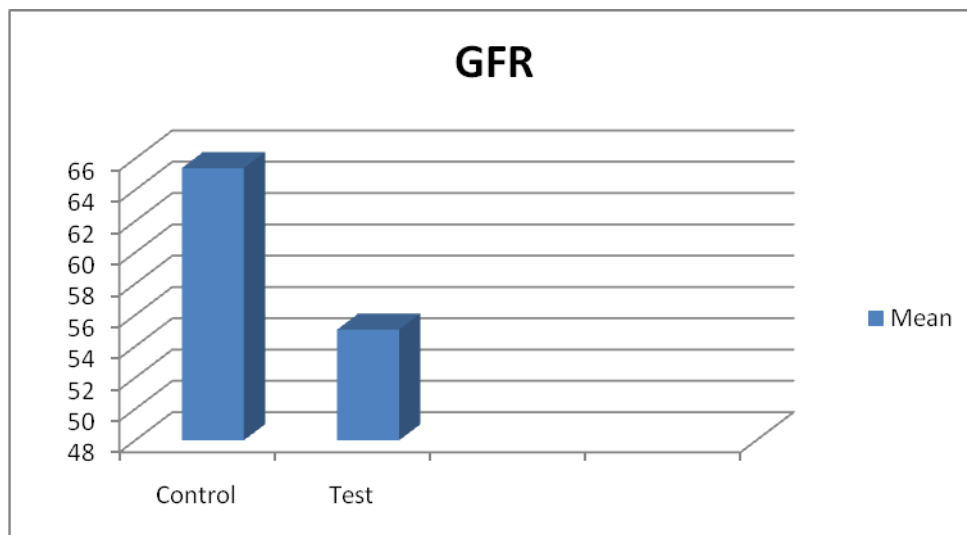**Fig.2** Creatinine levels of spironolactone and spironolactone with ARB

Fig.3 GFR levels of spironolactone and spironolactone with ARB

Conclusion

The results of this study suggest that usefulness of the Morisky scale for identifying patients who have been nonadherent with cardiovascular medications is limited in settings where the rate of nonadherence is low. Further research evaluating the Morisky scale should explore rewording questions and the use of graded response options. Drug-induced renal failure is the most important cause of increased potassium and creatinine levels in everyday clinical practice. Undetected hyperkalaemia may be suspected as a possible cause of sudden death in some patients treated for heart failure with spironolactone and angiotensin receptor blockers. Caution should be taken in elderly people. Most patients can and should benefit from the beneficial effects of these agents, but caution should be exercised especially in those with advanced kidney disease, heart failure, on renal replacement therapy, on potassium sparing diuretics and KCl replacement therapy. ARBs should be

discontinued once serum potassium exceeds 5.5 mEq/L, unless it can be controlled with diet, diuretics or sodium polystyrene sulfonate. Advice checking of serum creatinine and potassium level in one week after any change in spironolactone or ARB dosing.

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