RESEARCH GROUP IN KIDNEY DISEASES

RISK OF HYPERKALEMIA ASSOCIATED WITH THE USE OF BLOCKERS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN THE TREATMENT OF HEART FAILURE: A REVIEW

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Abstract
Heart failure (HF) is the leading cause of hospitalizations for cardiovascular diseases in Brazil. Hyperkalemia is an important adverse effect of therapy for HF. Several factors affect the incidence of hyperkalemia in patients treated for HF, as well as the presence of comorbidities and the use of associated medications. The aim of this study is to gather new evidence regarding the risk of hyperkalemia in patients treated for HF. The well-established therapy for HF involves drugs that may lead to hyperkalemia as inhibitors of angiotensin converting enzyme blockers, angiotensin II receptor blockers, aldosterone receptor blockers and direct renin inhibitors. The high incidence of HF in elderly patients with comorbidities such as diabetes mellitus and renal insufficiency increases the risk of hyperkalemia. Anti-inflammatory drugs, trimethoprim-sulfamethoxazole and heparin may aggravate the situation. Conclusion: Given the risk of hyperkalemia in patients undergoing treatment for HF, cautious monitoring of renal function and serum potassium should be performed.

Keywords: Hyperkalemia; Heart failure; Blockers of the renin-angiotensin-aldosterone system.

INTRODUCTION

The treatment of heart failure (HF) involves the use of blockers of the renin-angiotensin-aldosterone system (RAAS).[1-5] Aging, diabetes mellitus (DM), renal insufficiency and associated use of anti-inflammatory drugs (NSAIDs), heparin, and trimethoprim-sulfamethoxazole can induce hiperkalemia in heart failure patients treated with RAAS blockers.[6,7] The aim of this study is to gather new evidence regarding the risk of hyperkalemia in HF patients.

METHODS

This review article searched for original articles and guidelines in English on MEDLINE from 1998 to 2012 using the following keywords: hyperkalemia, heart failure, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists and direct inhibitor renin.

RESULTS

ACE inhibitors increase survival rates in patients with HF.[8-11] These drugs reduce systemic vascular resistance without increasing heart rate, decreasing rates of re-infarction and unstable angina, and improving the quality of life.[12-15]

According to the AHA Scientific Statement, Acute kidney injury (AKI) related to treatment with ACE inhibitors usually occurs at the beginning of therapy. This document recommends that the use of ACE inhibitors should be discontinued if there is a sustained increase greater than 50% in serum creatinine baseline or in case of hyperkalemia with serum potassium greater than 5.5 mEq/L.[16-18]

Angiotensin receptor blockers (ARBs)

The blockade of angiotensin II receptors may represent an important therapeutic strategy because it promotes more complete blockade of the RAAS, maintaining beneficial effects mediated by stimulation of AT2 receptors.[19-24]

The ELITE I study evaluated 722 patients randomized to receive treatment with captopril (50 mg) three times daily or losartan (50 mg) once daily, for 48 weeks, showing lower mortality in the group that used losartan. On the other hand, the ELITE II study evaluated 3132 patients and showed no difference between the groups treated with losartan or captopril related to mortality. There was a lower incidence of cough in the losartan group, whereas no difference was found between these drugs regarding the rates of AKI and hipercalemia.[25,26]

Aldosterone blockers

Spironolactone

Aldosterone is associated with an increase of fibroblast proliferation and perivascular fibrosis. Its blockade reduces collagen synthesis, improves cardiac function and prevents remodeling.[27-31] The RALES study showed a 30% reduction in mortality in the group treated with 25 – 50 mg of spironolactone as compared with placebo.[4] After its publication, several clinical studies have demonstrated the occurrence of hyperkalemia associated to the combination of ACE inhibitors and spironolactone for treating heart failure and serious clinical disorders were related to the increase in plasma levels of this electrolyte, including death.[31-40]

Eplerenone

Eplerenone is the first of a new class of drugs known as a selective blocker aldosterone receptor. It has minimal effect on steroid receptor, thereby minimizing the hormonal effects observed with spironolactone, such as ginecomastia.[41-44]

The EPHESUS study demonstrated a significant reduction in cardiovascular mortality and sudden death rates associated with the use of eplerenone. There was significant increase in the occurrence of severe hyperkalemia and decreased incidence of hypokalemia in the group treated with this drug.[45]

Betablockers

Beta blockers also favor the increase in serum potassium levels through two distinct mechanisms: blocking the stimulating action of the sympathetic nervous system on renin release and inhibition of the sodium-potassium ATPase, thus reducing cellular uptake of potassium.[8, 18]

Renin inhibitors

The study "Effects of the Oral Direct Renin Inhibitor Aliskiren in Patients With Symptomatic Heart Failure", conducted in 2008, concluded that aliskiren (150 mg / day) associated with the standard therapy of heart failure with ACE inhibitors (or ARBs) and beta-blockers appeared to be well tolerated and showed favorable neurohumoral effects, however there was no change in NYHA functional class of Heart Failure (HF), requiring new randomized controlled trials to prove the clinical efficacy and safety in HF.[46-48]

Predictors of hyperkalemia in HF patients

Chronic Renal Disease

Although demonstrate effective use of ACE inhibitors in patients with HF and chronic renal disease light to moderate, the CONSENSUS study showed no safety in patients with renal failure in advanced stages.[9]

The association of spironolactone with ACE inhibitors or ARBs should be avoided in patients in advanced stages of Chronic Renal Disease.[4, 39.40]

Advanced age

Important changes in the kidney have been described associated with aging, such as the progressive loss of nephrons, decreased glomerular filtration rate and reduced secretion of renin and aldosterone.[49-51]

Diabetes mellitus (DM)

Diabetic patients are more likely to develop hyperkalemia due to a decrease in insulin production, limiting the movement of intracellular potassium from the extracellular fluid.[40, 52]

Hyporeninemic hypoaldosteronism is associated with diabetes, decreasing sodium reabsorption and potassium excretion.[52]

Ahuja[53] retrospectively studied 119 patients using ACE inhibitors and found that 38.6% developed hyperkalemia. Of these, 96% had chronic renal disease and 84% were diabetic.

The association of DM and hyperkalemia has been described by other authors[54-55] with one case of a patient who developed severe hyperkalemia (8.9 mmol / L) 18 days after the beginning of the therapy with spironolactone and ACE inhibitors, with subsequent normalization of serum potassium after suspending drugs.

Vomiting and diarrhea

Schepkens et al. reported a serie of 25 patients with episodes of life-threatening hyperkalemia in patients treated with association of spironolactone and ACE inhibitors. Twelve of these patients showed signs of volume depletion associated with vomiting, diarrhea, infection and fever.[32]

Advanced heart failure

Svensson and col.[34] found that low ejection fraction of the left ventricle and advanced stages of heart failure were independent predictors of hiperkalemia.

Drugs related to hyperkalemia

Anti-inflammatory drugs (NSAIDs)

When in combination with ACEI, an exacerbation of hypoaldosteronism can occur, increasing the risk of hyperkalemia in these patients. This risk is also present with the combination of selective COX-2 and ACE inhibitors, so these drugs should be avoided in these patients.[18]

Heparin

Heparin causes hypoaldosteronism through a blocking of the synthesis of aldosterone by the adrenal increasing the risk of hypercalemia in patients using this drug, especially when associated with therapy for the treatment of IC.[18]

Sulfamethoxazole and trimethoprim (SMX-TMP)

A case-control study carried out in Ontario evaluated the risk of hyperkalemia in chronic users of spironolactone who had treated an urinary infection with TPM-SMX or nitrofurantoin or norfloxacin or amoxicillin. 165.754 patients with hyperkalemia on admission or during the course of hospitalization were analysed. The authors found a strong association between the use of TMP-SMX with the occurrence of hyperkalemia in these patients.[56]

The Table 1. shows the major publications that have identified risk factors associated with hyperkalemia.

Table 1 – RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF HYPERKALEMIA

Reference	Publication	N	Predictors of hyperkalemia	Hyperkalemia (%)
RALES[4]	1999	1663	Age, NYHA Heart Failure Class III-IV, drugs	1,4%
Schepkens & Vanholder[32]	2001	262	Age, Renal Disfunction, DM* and NHAIS[4]	9,5%
Berry & McMurray[33]	2001	4	Diarrhea and pre-renal azotemia	100%
Svensson & Gustafsson[34]	2003	108	Age, Renal Disfunction and Low ejection fraction of the left ventricle	12%
Wrenger & Müller[37]	2003	44	Age, Renal Disfunction and DM*	100%
Bozkurt & Ildiko[35]	2003	104	Renal Disfunction and DM*	11,5%
Cruz & Marcílio de Souza[36]	2003	49	Renal Disfunction, DM* and NYHA Heart Failure Class IV	14,2%

McMurray & Pitt[48]	2008	302	HAS[x], NYHA Heart failure Class II-IV, [#]BNP, aliskiren	5,6%
Henz & Maeder[57]	2008	10.320	Age, Renal disfunction, DM[*] and drugs	5%
Antoniou & Gomes[56]	2011	165.754	Age, spironolactone and [§]SMT-TMP[4]	10,8%

[*] Diabetes Mellitus; [x] Systemic Arterial Hypertension;

[#] Brain natriuretic peptide; [§] Trimethoprim-sulfamethoxazole.

Prevention of Hyperkalemia

Spironolactone or its combination with ACE inhibitors or ARBs are not recommended in patients with potassium > 5.0 mmol / L or creatinine clearance <60 mL/min.[39,40,57,58]

Introducing ACE inhibitor at low doses and monitoring serum creatinine and potassium in the first 15 days is recommended.[32-37] In case of good tolerance to ACE inhibitors or ARBs, spironolactone therapy must be added in a dose up to 25 mg/day.[16,39,40] The monitoring of renal function and serum potassium should be performed after the introduction of new drugs, dose changes and in case of clinical conditions that decrease renal perfusion, such as diarrhea, vomiting or worsening of heart failure.[32, 33]

CONCLUSION

Close monitoring of renal function and serum potassium should be performed in patients at the beginning and during the treatment of heart failure.

Further studies should be encouraged using a sample more similar to the "real world" for better establishment of safety associations regarding to the use of RAAS inhibitors to treat heart failure.

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