Influence of Spironolactone Therapy on Thiamine Blood Levels in Patients with Heart Failure

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Summary

Background: The nonpharmacological management of heart failure (HF) has been understudied. The importance of micronutrients such as thiamine has long been known since its deficiency is associated with the development of high-output HF.

Objective: We studied the relationship between adding to ACE inhibition further aldosterone suppression with spironolactone and thiamine blood levels (pmol/ml).

Methods: A total of 22 patients (pts) with HF (NYHA III/IV) were divided in two groups [group I-spironolactone 25mg/qd (n=11) and group II – no spironolactone (n=11)]. Thiamine levels were determined using the erythrocyte transketolase activity. The groups were compared regarding food intake, demographics, furosemide doses and thiamine blood levels using Mann-Whitney and student's T-test. The proportions were analyzed with Chi-square and Kruskal-Wallis tests to associate thiamine with demographics and furosemide doses as dependent variables.

Results: Group I and II were similar regarding food intake, daily furosemide doses (110.9±30.2 and 105.5±26.9 mg, respectively; p>0.05), demographics (etiology, age, hypertension, diabetes, smoking, alcohol abuse, dyslipidemia and adjuvant drug HF treatment). Pts in group I showed significantly higher thiamine levels when compared to pts in group II (277.2±89.8 and 154.7±35.7, respectively) (p<0.001). None of the dependent variables cited above were associated with thiamine.

Conclusion: In a cohort of ambulatory HF patients on high dose of loop diuretics, the use of spironolactone is associated with higher thiamine blood levels. The significance of this finding remains to be established by future studies with prospective design and larger sample sizes. (Arq Bras Cardiol 2008; 90(5): 324-328)

Key words: Spironolactone/therapeutic use; thiamine/blood; cardiac output, low.

Introduction

Decompensated heart failure (DHF) is a highly prevalent entity and leading cause of death and hospitalizations in industrialized countries[1-3].

The adverse role of increased levels of aldosterone in DHF pathophysiology has been definitely established.

In addition to its classic mineralocorticoid properties resulting in salt and water retention, aldosterone has effects on vascular remodeling, endothelial-cell and baroreceptor dysfunction, reduces heart-rate variability, inhibits myocardial norepinephrine uptake and induces cardiac fibrosis[4-10].

This has led to the strategy of neuro-humoral suppression in the management of heart failure and the clinical significance of adding an aldosterone antagonist (spironolactone) to the DHF drug regimen was demonstrated in the Randomized Aldactone Evaluation Study (RALES) with a 30 % reduction in mortality[11].

The nonpharmacological management of DHF though has been understudied and while a high sodium diet is in general considered detrimental little is known about other micronutrients such as vitamins. Thiamine (vitamin B1) is classically linked to cardiovascular disease since its deficiency leads to a well known form of high-output heart failure (Beri-Beri disease) which is potentially reversible once thiamine blood levels are restored.

The use of high dose loop diuretics in DHF patients is associated with spoliation of thiamine reserves and has been reported since the late 70s[12-16]. In one of these studies[14] the thiamine replacement caused a mean 13% increase in left ventricular ejection fraction.

In a previous study[17], it was observed a possible effect of spironolactone as a saver of thiamine spoliation induced by furosemide.

Therefore this study was designed to investigate the relationship

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between thiamine blood levels and the use of spironolactone in patients with moderate to severe chronic heart failure.

Methods

Study design

This is a cross-sectional observational study with twenty-two patients followed in a cohort of an ambulatory HF clinic in a tertiary university hospital. Patient data collection was carried between July 2001 and September 2001. Ambulant patients of either sex, aged between 48 and 81 years, with symptoms and objective evidence of chronic heart failure (left ventricular ejection fraction of <0.40 and pulmonary venous congestion and/or edema) were eligible to enter in the study. All patients were in heart failure class (NYHA) III or IV. All patients were using high dosis of furosemide (>80mg/day) and ACE inhibitors, and the majority of patients were taking beta-blockers.

Habitual food intake was assessed using a validated semiquantitative food frequency questionnaire, but there are no validated questionnaires for thiamine intake assessment. Subjects were asked about 60 food items. Food pictures were used for identification of the foods. Each food had a corresponding serving portion, and each serving portion had a corresponding weight. The amount of foods consumed was quantified by multiplying the daily frequency of consumption by the number of serving portions consumed and their corresponding weights. A qualitative question (with yes or no responses) was used to assess vitamin supplement intake. Patients also answered a questionnaire regarding concomitant diseases (celiac sprue, causes of intestinal malabsorption, presence of chronic diarrhea, and chronic illness such as neoplasia), current alcohol abuse and previous surgeries to avoid confounding variables. Others exclusion criteria were renal failure (serum creatinine > 2.5mg/dl) and caquectic patients.

All participants provided their written informed consent to take part in the study, and the Local Ethics Committee approved the study protocol, including the blood collection.

Demographics were registered (etiology of heart failure, sex, hypertension, diabetes mellitus, smoking, and hypercholesterolemia) along with current medical therapy such as furosemide.

Patients were divided in two groups according to use of spironolactone: 1) group I - on spironolactone use (25mg po qd) and 2) group II - without spironolactone use and were subsequently compared regarding food intake, demographics and thiamine blood levels and the groups were paired by age, sex and skin color.

Biochemical assessment of thiamine blood levels

Between 8 am and 10am, after an overnight fast, venous blood (6 mL) was collected from each subject into tubes containing EDTA. After collection, the blood specimens were immediately placed in a dark cool box until they arrived at the laboratory. Hemoglobin concentration was determined within 2–3 h after blood collection. Hemoglobin analysis was carried out using the cyanomethemoglobin method (INACG 1985). Thiamine status was determined by measuring the erythrocyte transketolase (ETK) activity[18,19].

The basal ETK activity and its activity after adding thiamine pyrophosphate (TPP) were used to calculate the TPP effect, which is considered to be an indicator for thiamine status. The coefficient of variation for basal ETK activity is 5% for both within- and between-day analyses. The corresponding values for ETK activity are 2 and 4%, respectively. The measurements of erythrocyte TPP used the apoenzyme recombination concept and are displayed in pmol/ml[20].

Statistical analysis

Data are presented as the mean±SD.

Study groups were compared regarding food intake, demographics, furosemide doses and thiamine blood levels using student's T-test or Mann-Whitney test. The proportions were analyzed with Chi-square and Kruskal-Wallis tests to associate thiamine levels with demographics and furosemide doses as dependent variables. We did not include a multivariate analysis because it was not necessary.

Considering that patients on spironolactone use (25mg po qd) should have 25% higher thiamine blood levels than the other group, we needed 10 patients in each group to have 95% of confidence interval (α=0.05) and 80% of power (β=20%).

Results

A total of 22 patients (pts) were enrolled aged 48-81 (62.6±8.6 y/o). Patients baseline characteristics are as follows: 15 pts (68.2%) were men, 13 pts (59.1%) had hypertension, 8 pts (36.4%) had diabetes mellitus, 7 pts (31.8%) were smokers, zero pts (0%) admitted to alcohol abuse, 6 pts (27.3%) had hypercholesterolemia. The patients were moderately to severely symptomatic [NYHA class: III-14 pts (63.6%); IV-8 pts (36.4%)]. Ischemic heart disease was the most common cause of HF (11 pts - 50.0%) followed by hypertension (7 pts-31.8%), idiopathic (2 pts-9.1%) and alcohol (2 pts-9.1%) etiologies. Adjuvant HF drugs at the time of enrollment included ACE inhibitors (22 pts-100%), beta-blockers (19 pts – 86.3%), diuretics (22 pts-100%), digitalis (7 pts-31.8%), amiodarone (2 pts-9%) and nitrates (11 pts-50%).

Group I was comprised of 11 pts (50.0%) and group II of 11 pts (50.0%). When comparing groups I and II using the variables cited above there was no significant statistical difference including daily doses of furosemide (mg) (110.9±30.2mg and 105.5±26.9mg, respectively; p=0.66) (figure 1), doses of ACE inhibitors (mg) (captopril; group I - 97.7±68.9mg and group II – 86.4±49.2mg; p> 0.05), other adjuvant HF drug treatment or dietary thiamine intake. The most important characteristics of both groups were described in table 1.

Patients on spironolactone therapy (group I) showed significantly higher thiamine blood levels when compared to patients in group II (277.2±89.8 pmol/ml and 154.7±35.7 pmol/ml, respectively) (p<0.001) (figure 2).

Discussion

The importance of adequate nutrition in chronic cardiac disease states and its prognostic value has long been known[21,22].

Amongst different nutrients vitamins as a group have much been studied having different contributions in cardiovascular disease[16].

Thiamine is a water-soluble, B-complex vitamin; when thiamine is phosphorylated to thiamine diphosphate (ThDP), functions as a cofactor for enzymes that catalyze α-keto acid decarboxylation or formation and cleavage of α-hydroxy ketoses[23].

Thiamine plays an important role in the myocyte contraction as shown in experimental animal models[13]. Its deficiency can result from malnourishment or alcohol abuse leading to impaired oxidative metabolism and high-output heart failure (Beri-Beri disease) due to the accumulation of piruvate and lactate leading to intense vasodilation[15]. Response to restoration of thiamine body stores is often with full recovery and low whole blood levels has been reported in patients on chronic use of loop diuretics[12,14].

An Brazilian study showed that thiamin deficiency was observed in 33% of the patients with heart disease compared to 10% of the control individuals (p=0.02)[24].

Its supplementation in HF patients on chronic high dose diuretics resulted in improvement in left ventricular ejection fraction and rise in systolic blood pressure[25].

Aldosterone blockage strategy through different drugs remains cornerstone in HF treatment. The present study addresses the relationship of adding to ACE inhibition further aldosterone antagonism with spironolactone and thiamine blood levels. In the group receiving spironolactone, thiamine blood levels were significantly higher. None of the other variables studied had any relation with thiamine blood levels. This raises the question of a potential relationship between aldosterone suppression and increased thiamine intestinal absorption and/or decreased renal excretion.

Thiamine in the intestinal lumen is in free form and very low concentrations. The entry of thiamine into the enterocyte is completely inhibited by thiamine analogs and reduced by ethanol administration. Outwardly oriented H^+ gradients enhance thiamine transport, whose saturable component is a Na^+-independent electroneutral uphill process utilizing energy supplied by the H^+ gradient, and involving a thiamine/ H^+ 1:1 stoichiometric exchange. The exit of thiamine from the enterocyte, as evaluated in basolateral membrane vesicles, is Na^+-dependent, directly coupled to ATP hydrolysis by Na^+-K^+-ATPase. Transport of thiamine by renal brush border membrane vesicles is similar to the intestinal as far as both H+ gradient influence and specificity are concerned[26].

Table 1 - Demographics characteristics per group

Characteristics	Group I – with spironolactone (n=11)	Group II – without spironolactone (n=11)	p
Gender % (n)			
Male	72.7 (8)	63.6 (7)	1.0
Female	27.3 (3)	36.4 (4)	
Skin color % (n)			
White	81.8 (9)	45.5 (5)	0.183
Non-white	18.2 (3)	54.5 (6)	
NYHA Functional Class (FC) % (n)			0.659
FC III	54.5 (6)	72.7 (8)	
FC IV	45.5 (5)	27.3 (3)	
Hypertension % (n)	72.7 (8)	45.5 (5)	0.387
Diabetes Mellitus % (n)	36.4 (4)	36.4 (4)	1.0
Furosemide doses > 120mg/day % (n)	45.5 (5)	45.5 (5)	1.0
Beta Blocker use % (n)	81.8 (9)	90.9 (10)	1.0
ACEI use % (n)	100 (11)	100 (11)	1.0

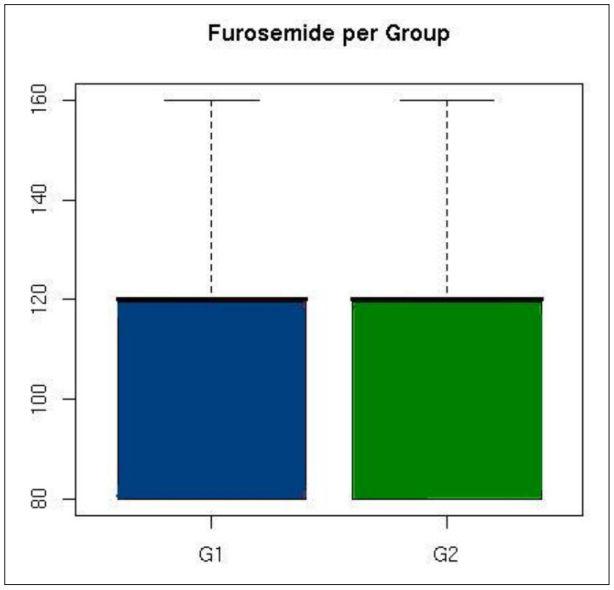

Figure 1 - Furosemide doses per group (p=0.66).

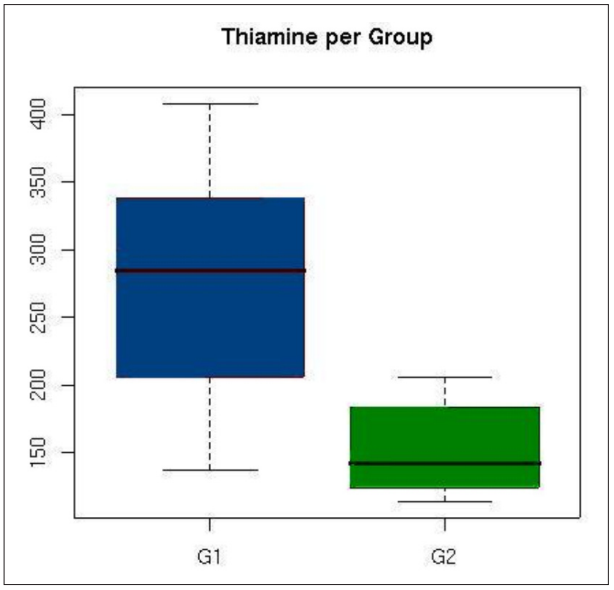

Figure 2 - Thiamine blood levels per group (pmol/ml) (p<0.001).

There is strong evidence for the presence in rat renal brush border membrane vesicles of a thiamin/H^+ antiport having a 1:1 stoichiometric ratio[27].

Aldosterone's effects seem to be partly mediated by controling ion transport through cell membrane proteins such as Na^+/ H^+ antiporter and transcriptional regulation of Na^+/K^+–ATPase synthesis[28-30].

Therefore, a possible link between suppression of aldosterone effects and reduced thiamine spoliation in HF patients in use of high doses of loop diuretics might exist.

Thiamine replacement resulted in improvement in left ventricular ejection fraction and rise in systolic blood pressure[25]. So we can raise the possibility that its systematic replacement might contribute to a better myocardial performance in patients taking diuretics for a long time and spironolactone use can improve these results.

Based on these data, we developed a new prospective, randomized, controlled study with a large sample size with three groups (spironolactone plus furosemide, placebo plus furosemide and no diuretics use) to confirm our hypothesis and that is concluding the final analysis.

Study limitations

The main limitation of the present study derives from its small sample size along with its cross-sectional observational design. For these reasons our results must be considered hypothesis-generating rather than conclusive.

Conclusions

In a cohort of ambulatory HF patients on high dose of loop diuretics the use of spironolactone is associated with higher thiamine blood levels. The significance of this finding remains to be established by future studies with prospective design and larger sample sizes.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

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