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Congestive heart failure and ventricular arrhythmias in relation to serum magnesium

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Summary
Congestive Heart Failure (CHF) is associated with biochemical evidence of electrolyte imbalance including magnesium deficit, which may increase myocardial electrical instability, risk of malignant arrhythmias and sudden death. The aim of this study was to determine serum magnesium concentration in 45 patients (Group I; 24 male, 21 female; the average age 49.7 years) with CHF, New York Heart Association (NYHA) Class II, III who were treated with lisinopril [Angiotensin–Converting Enzyme Inhibitor (ACEI)], frusemide (diuretic) and digoxin. All patients were subjected to resting 12-lead electrocardiography (ECG) and ventricular arrhythmias were analysed in relation to serum magnesium concentration at baseline and at end of the fourth week of treatment. Control group (Group II; 24 male, 21 female; the average age 49.3 years) were matched with Group I. Serum magnesium was determined by Atomic Absorption Spectrophotometer (AAS). Statistical analysis was with Student's t-test. It was observed that 6 (13.3%) CHF patients had ventricular arrhythmias at the commencement of the study. This number increased to 17 (37.8%) by the end of the fourth week of treatment. At four weeks, there was significant difference in serum magnesium between CHF patients without arrhythmias ($0.69 \pm 0.11 mmol.L^{-1}$) and those with arrhythmias ($0.50 \pm 0.01 mmol.L^{-1}$), $P < 0.0001$. Results obtained suggest that CHF patients having hypomagnesemia had higher prevalence of ventricular arrhythmias. It should be stressed, however, that 24 hour ECG monitoring and classification of ventricular arrhythmias according to Lown may give a more accurate picture. Nevertheless, routine serum magnesium assays, as part of the electrolyte profile of CHF patients would assist in early prevention and detection of magnesium depletion. This would go a long way to reduce the susceptibility to lethal arrhythmias and sudden death.

Keywords: *Congestive heart failure, ventricular arrhythmias, sudden death.*

Résumé
Le Defant de Congestion du Coeur (DCC) est associe au desequilibre electrolyte a evidence biochimique, incorporant le deficit de magnesium, qui pourrait augmenter l'instabilite electrique myocardiaque misque de l'arrhytmiase malique, et mort subite. The but de cette etude etait de determiner la concentration du serum - magensium chez 45 patients (Groupe I; 24 hommes, 21 femmes, age moyen 49, 7 aus) avec DCC, Association New Yorkaise de coeur (ANYC), class II, III ont ete traitees avec lisinopril [Angiotensine - convertissant l'Enzyme Inhibiteur (ACEI)] frusemide (diuretics) and digoxin. Tous les males ont ete soumis a 12 repos electrocardiographique (ECG) et l'arrhythmiase venticulaire etait analysee eu relation a la concentration du serum - magnesium a la ligne de base, et a la fin de la quatrieme semaine de traitement. Groupe de controle (groupe II, 24 hommes, 21 femmes; age moyer 49, 3 aus) ont ete jumeles au groupe I. La quantite et la qualite du serum - magenesium a ete determinee par absorption atomique du spectrophotometre. L'analyse statistique a ete realisee par le student's t-test (t - test de l'Etudiant). Il a ete observe que 6 (13, 3%) patients DCC avaient l'arrhytmiase ventriculaire au debut de l'etude. Ce nombre a augmente jusqu' a 17 (31, 8%) a la fin de la quatrieme semaine, il ya eu changement significatif en serum - magnesium entre patients DCC sans arrhytmiase ($0, 69 \pm 0,01 mmol.L^{-1}$), $P < 0,0001$. Les resultats obtemus suggerent que les patients DCC ayant l'hypomagnesemia ont une prevalence elevee de l'arrhytmiase ventriculaire. Il doit entre soulique, cependant, que 24 heures de controle ECG et classification de l'arrhytmiabe ventriculaire selon lown pent donner une figure plus precise. Neanmoins, la qualite et quantite du serum - magenesium, comme partie du profil electrolyte des patients DCC pourait assiter dans la prevention et la detection de l'epuisement du mangnesium. Ceci pouma a long terme, reduire la susceptibilite de l'arrhytmiase lethale et la mort subite.

Introduction

Congestive Heart Failure (CHF) is a principal complication of virtually all forms of heart disease and it results in poor life expectancy in comparison to the total population [1]. There is a high incidence of ventricular arrhythmias and sudden death in CHF patients occurring in more than 40% of total cardiac deaths [2]. Despite improvement in management, CHF proves to be extremely lethal and the poor prognosis remains till today. It imposes a large economic burden on the patient, his relations, the health care budget, and as such, it is costly to the larger society. Ventricular arrhythmia is an indicator of risk of sudden death, thus, it is a possible target for preventive measures [3,4]. Apart from being an independent risk factor for poor prognosis, low serum magnesium level has been associated with higher prevalence of ventricular arrhythmias[5]. Magnesium is important in preserving electrical stability of myocardial cells. It controls and modulates calcium entry and release from the sarcoplasmic reticulum and maintains flux of cellular potassium across the sarcolemma [6,7].

CHF provides the perfect medium for the development of electrolyte disturbances. Elevation of neurohumoral chemicals, including the renin-angiotensin-aldosterone axis, diuretic and digitalis therapy represent the major contributory factors [8.9].

This study was performed to determine concentrations of magnesium in sera of patients undergoing treatment for CHF. The results were then correlated to arrhythmias in the patients.

Patient population and methods

Forty-five (45) patients (group I) with CHF comprising 24 males, 21 females, of average age 49.7 years (range 17 to 82

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response to magnesium treatment provides much of the evidences. Hypomagnesemia aggravates digitalis toxicity and arrhythmias develop at a lower dose and persisted longer [27]. It can be hypothesized that a reduction of membrane Na^+K^+-ATPase activity is caused by hypomagnesemia. In turn, this results in loss of potassium from the intracellular space, causing a change in the ratio of intracellular to extracellular potassium. Since this ratio largely determines the resting membrane electrical potential, the consequences of an alteration are increased cellular electrical excitability and greater tendency to reentry arrhythmias and aberrant conduction.

Other possible mechanism include direct electrophysiologic effect, or through effect on calcium metabolism. Extracellular magnesium exerts a stabilizing effect on the sinuatrial node and atrial muscles. Magnesium deficiency shortens the absolute refractory period but extends the relative refractory period. This means that the duration of the vulnerable period is increased, resulting in a greater risk of arrhythmias [28]. Magnesium has also been closely related to calcium metabolism and is considered as nature's calcium blocker [29]. Magnesium deficiency leads to influx of calcium into myocardial cells. There is also failure to extrude calcium out of the cells through magnesium dependent Ca^{++}-ATPase activity. The sarcoplasmic reticulum fails to sequestrate the excess calcium. This results in increased intracellular calcium that gives rise to oscillatory after potentials, and arrhythmias.

Preventing CHF patients from magnesium deficit is the first, and the application of magnesium supplement is the second best strategy to help keep them free from life-threatening arrhythmias. Pharmacological approach to the reduction of risk of sudden death may include magnesium supplementation. It is simple, cost-effective and safe. Prospective randomized placebo-controlled studies are needed to assess the role of magnesium and the effects of magnesium supplementation in CHF patients.

Conclusion

1. The study showed that at the end of four weeks of treatment, CHF patients had reduced serum Mg levels compared to the levels before treatment and levels in control subjects.
2. The study seems to suggest an increased prevalence of cardiac arrhythmias in hypomagnesemic CHF patients.

Study limitations

Our ECG recordings were not ambulatory. The study did not assess whether ventricular arrhythmias in subjects with low magnesium levels were associated with mortality risk.

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years) were studied. The causes of CHF included, hypertension (22), Dilated cardiomyopathy (13) and rheumatic valve disease (10).On the first day of entry into the study ,8 patients were classified into New York Heart Association (NYHA) functional Class II and 37 patients into functional class III; each having signs of left ventricular systolic dysfunction on echocardiography (echo). No patient had any other disease causing electrolyte disturbances and none was on therapeutic potassium or magnesium supplements. The experimental protocol was approved by the joint University College Hospital and University of Ibadan Ethical Committee. All subjects gave informed consent.

Depending on the clinical features, 19 patients were treated with Lisinopril; 16 with frusemide and 10 with Digoxin. All patients were subjected to a resting 12-lead electrocardiography (ECG), MacVu marquette ALFXXG resting ECG analysis system at baseline and end of the fourth week of study. Resting ECG abnormalities were defined as any deviation from normal, including non-specific ST-T wave changes, arrhythmias and conduction abnormalities. Only the ventricular arrhythmias were analysed in relation to serum magnesium concentration irrespective of treatment.

The control (Group II) consisted of 45 healthy subjects (24 males and 21 females) of average age 49.3 years (range: 15 to 85 years). Routine physical examination, ECG and echo for the control group were in the normal range.

Peripheral venous blood was obtained from each patient and control subject at baseline and at the end of fourth week of study. Sera were separated by centrifugation at 1,000rpm and stored at -20°C till seroanalysis in a research laboratory. Potassium in the serum was determined by flame photometry[10]. Serum magnesium was assayed using atomic absorption spertrophotometry[11] (model Buck Scientific Atomic Absorption/Emission Spectrophotometer). The serum samples were diluted 1 in 50 (0.1ml to 5 in 0.2 percent lanthanium oxide). The standard magnesium solutions were diluted in the same manner and used to calibrate the spectrophotometer. The AAS was fitted with Mg hollow cathode lamp set at wavelength 285.2 nM. The samples were nebulized with argon carrier gas at 7l.min^{-1}. Standard solutions for Mg^{2+} were prepared from analar grade salts (BDH chemicals). Students t-test was used for statistical analysis.

Results

Serum potassium concentration in CHF patients was 3.8 ± 0.3 mmol.L^{-1} at baseline and 3.6 ± 0.5 mmol.L^{-1} at end of 4 weeks $P > 0.1$. In the control group, serum potassium concentration was 3.9 ± 0.5 mmol.L^{-1} at baseline and 4.2 ± 0.7 mmol.L^{-1} at end of 4 weeks $P > 0.1$.

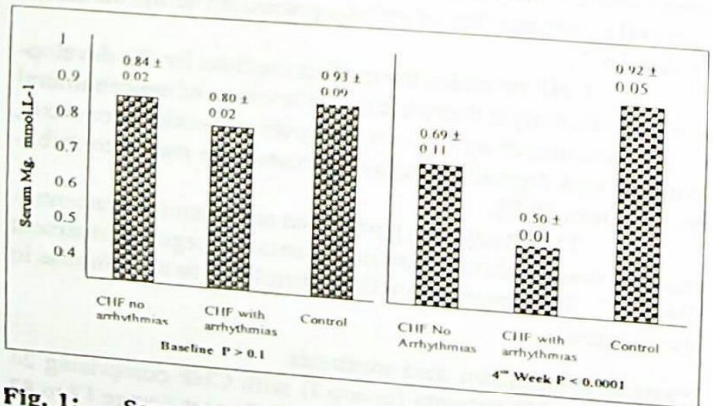

Fig. 1: Serum Magnesium concentrations and arrhythmias in patients with CHF.

The relationship between serum magnesium and arrhythmic status are summarized in the figure . After adjusting for serum potassium concentration using analysis of covariance, there was no statistically significant difference in the adjusted group means of serum magnesium. At baseline, the adjusted mean serum magnesium of CHF patients without arrhythmias (0.84 ± 0.02mmol.L^{-1}) was not significantly different from that of the controls (0.93 ± 0.09mmol.L^{-1}), $P > 0.1$. It was also not significantly different from those with arrhythmias (0.80 ± 0.02mmol.L^{-1}), $P > 0.1$. However, at the end of the fourth week, there was a statistically significant difference in the adjusted means of serum magnesium between CHF patients without arrhythmias (0.69 ± 0.11mmol.L^{-1}) and those with arrhythmias (0.50 ± 0.01mmol.L^{-1}), $P < 0.0001$. This result shows that patients having arrhythmias had lower levels of serum magnesium than those who did not. At the commencement of treatment, the difference in serum magnesium was not significant, $P > 0.1$. However, four weeks after treatment, the serum magnesium decreased in all patients but significantly lower in patients with arrhythmias, $P < 0.0001$. It was observed that 6 (13.3%) CHF patients had arrhythmias at the commencement of the study. This number increased to 17 (37.8%) by the end of four weeks of treatment. The arrhythmias observed were ventricular premature complexes (VPC) which could be occasional, fusion complexes, aberrant complexes or multiform.

Disucussion

CHF is one of the main reasons for hospitalization in patients with cardiovascular diseases in our environment [12,13]. Once heart failure has occurred, there is a high mortality rate with an incidence of sudden death of nearly 50% [1,2].

The relationship between ventricular arrhythmias and survival has been studied in recent years since sudden deaths in CHF patients may be associated with ventricular arrhythmias resulting from electrolyte imbalance [4,14,15]. The mechanisms of these arrhythmias are still poorly defined, however, potassium and magnesium are important contributory factors[16-18]. Although, it has long been recognized that potassium imbalances can contribute to arrhythmogenesis, the role of magnesium in this setting has only recently become a focus of study. There are conflicting data regarding the impact of serum potassium and magnesium levels on the occurrence of ventricular arrhythmias in the clinical setting [17,19]. The clinical evidence for the association of magnesium levels with ventricular arrhythmias include small clinical studies [18,20,21] and studies with inadequate control [22,23]. Studies involving a large number of subjects especially those without major structural heart disease are few [5].

In this study, there appears to be an association between hypomagnesemia and arrhythmias and this is consistent with the results of previous studies [5,21,24]. However, some clinical studies have not confirmed the association of low serum magnesium with the occurrence of ventricular arrhythmias [17,18,22,23]. The patients used in the present study did not have 24-hour Holter monitoring to quantify the number of VPCs per hour as was done in these studies and this may account for inaccurate estimation of the relationship between hypomagnesemia and ventricular arrhythmias. Nevertheless, there is growing evidence from a number of case reports that magnesium deficiency is a factor in the development of various tachyarrhythmias [26,27]. The resistance of these arrhythmias to conventional therapy and the positive

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