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Serum and urinary magnesium during treatment of patients with chronic congestive heart failure

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Summary
Electrolyte disturbances are common in patients with Congestive Heart Failure (CHF) especially during long-term treatments. Unlike potassium, little is known of how magnesium is affected in these patients. This study was carried out to determine the serum and urinary concentration of magnesium in patients with CHF who were treated with lisinopril [Angiotensin- Converting Enzyme Inhibitor (ACEI)], frusemide (diuretic) and digoxin, at baseline, 2 weeks and 4 weeks. 45 patients (Group I; 24 male, 21 female; average age 49.7 years) with CHF, New York Heart Association (NYHA) Class II, III were matched with 45 healthy controls (Group II; 24 male, 21 female, average age 49.3 years). Serum and urinary magnesium were assayed by atomic absorption spectrophotometer. Statistical analysis was made by Student's t-test. At baseline, serum magnesium concentration in CHF patients was not significantly lower than in controls, $p > 0.1$. However, a higher loss of magnesium in urine was found in CHF patients compared with control subjects at baseline, $p < 0.01$. Serum magnesium concentration decreased significantly during treatment except in CHF patients on lisinopril, $p < 0.05$. The lowest excretion of magnesium was also found in this group of patients. Our study shows that lisinopril is magnesium-sparing in patients with CHF.

Keywords: *Magnesium, congestive heart failure, serum, urine* .

Résumé
Les troubles electrolytes sont frequents chez les malades sonffrant du defaut de surcharge du coeur (CHF) speciallement au conrs de long traitements. Contrairement au potassium, on conmait tres peu l'effet du magnesium chez les patients. Cette etude a ete faite pour determiner la concentration urinaire du serum et du magnesium chez le malades CHF traites au lisinopril [Angiotensine - Convertissant l'enzyme inhibiteur (ACEI)], frusemide (diuretique) et digoxine, a la base, 2 a 4 semaines. 45 malades (Groupe 1, 24 hommes et 21 femmes; age moyem 49,7 aus) avec CHF, Association New Yorkaise de coeur (NYHA) classes II, III out ete jumelees avec 45 cas de controle naturel. (le groupe II est compose de 24 hommes et 21 femmes, age moyen 49, 3 aus). Le serum et le magnesium urinaire out ete analyses qualitativement et quantitativement par absorption atmoque du spectrophotometre. L'analyse statistique a ete realisee par le t-test de l'Etudiant. A la base, la concentratim du serum-magnesium chez les CHF n'etait pas significativement basses comparee a ceux des controles, $P > 0,1$. Nean moins, a une grande perte de mangensium daus l'urine a ete notee chez les malades CHF, comparee a ceux des controles a la ligne de base, $P < 0,.01$. La concentration du serum et magnesium diminue significativement, excepter chez les malades CHF sur traitement au lisinopril, $P < 0,05$. La plus petite excretion du magnesium etait aussi notee chez les patients de ce groupe. Notre etude montre que la lisinopril est magnesium - eparguant chez les malades sonffrant de CHF.

Introduction

Congestive Heart Failure (CHF) represents a complex clinical syndrome characterized by abnormalities of ventricular function and compensatory neurohumoral mechanisms, which are accompanied by effort intolerance, fluid retention, and reduced longevity [1]. Neurohumoral reaction in CHF affect electrolyte balance [2,3] . Magnesium, an essential cation, has recently been receiving considerable attention in clinical medicine, especially regarding its role in cardiovascular pathophysiology [4]. Magnesium deficiency has been implicated in the pathogenesis of atherosclerosis, arterial hypertension, myocardial infarction, dysrhythmias, and cardiomyopathies [5,6]. It has been speculated that magnesium losses occur following diuretic treatment of patients in CHF, especially long-term [7]. Magnesium homeostasis is implicated in digitalis intoxication [8] while the effects of ACEI is unclear [9,10]. Very little attention has been paid to clinical implications of Magnesium deficiency which is an independent risk factor for poor prognosis in patients with CHF [11,12]. This may be due in part to the lack of routine serum magnesium analysis as part of the electrolyte profile requested by physicians thus impeding the diagnosis of clinical magnesium depletion in such patients. Also, the technology for this procedure although simple, is not readily available in most of the diagnostic laboratories.

This study was performed to determine the serum and urinary magnesium concentrations in a selected population of CHF patients, and to relate this to different drug treatments.

Methods

Patient population

Forty-five patients (24 males, 21 females) of average age 49.3 years (range 17 to 82 years) fulfilling Framingham Criteria for CHF [13], New York Heart Association (NYHA) functional classes II and III were studied. At the time of hospitalization, 8 patients with symptoms of heart failure were classified as functional class II and 37 patients as functional class III, each having clinical and echocardiographic (echo) signs of left ventricular systolic dysfunction. No patient was on therapeutic magnesium or other electrolyte supplements, and none had any other disease associated with electrolyte disturbances or malabsorption. Because myocardial infarction and intrinsic renal dysfunction may alter magnesium metabolism, patients with evidence of occlusive coronary artery disease or serum creatinine level greater than 1.5 $mg.dl^{-1}$ were excluded from the study. The experimental protocol was approved by the Joint University College Hospital and University of Ibadan Ethical Committee. All subjects gave informed consent.

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the reduction in urinary magnesium excretion, so that the obligatory urinary loss may be reduced to less than 1.5 mmol.day^{-1} when dietary magnesium is severely restricted [19,20]. With the impaired alimentary absorption expected in CHF, persistent renal loss caused by diuretics, and elevated circulating levels of aldosterone and vasopressin, the increased excretion of magnesium in the presence of hypomagnesemia is not too surprising.

Serum magnesium concentrations in this study were significantly altered by treatment, with the exception of patients on lisinopril. Lisinopril has a potassium sparing action [21], but little is known of how it influences magnesium stores in the body. Some studies have shown that treatment with ACEI results in normal to increased levels of magnesium and potassium in serum and tissues such as erythrocytes [22] and muscle [23] in patients with CHF. Our study also shows that CHF patients on lisinopril with or without diuretics had no significant reduction of serum magnesium, thus suggesting a beneficial effect. This group also had the lowest concentration of urinary magnesium.

Patients receiving frusemide, and those on frusemide-digoxin combination had significant decrease of serum magnesium with time. They also had the highest excretion of magnesium in the urine. It has been reported that loop diuretics and long-term treatment with thiazide diuretics can decrease serum magnesium and potassium, while potassium-sparing spironolactone tends to increase them [24,25].

We concluded that the prevalence of hypomagnesemia in CHF patients was higher compared with age and sex-matched controls. Lisinopril treatment appears to be magnesium/sparing ,whereas, diuretics and diuretic-digoxin treatment caused significant urinary magnesium loss. However, intracellular to extracellular magnesium ratio may be more relevant in the pathophysiology of CHF than absolute serum levels because it is possible for magnesium depletion to occur in the presence of normal serum magnesium concentrations For this reason, routine serum magnesium analysis should be included as part of the electrolyte profile in the management of patients with CHF. Also, long-term oral magnesium replacement and/or supplementation may be considered especially in those who are not predisposed to magnesium retention from other disease states.

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References

1. Braunwald E, Colucci WS and Grossman W: Clinical aspects of heart failure: High-output failure, pulmonary edema. In Braunwald E. (ed.): Heart Disease, 5th ed., Saunders WB Co. 1997; 445.
2. Wester PO. Electrolyte balance in heart failure and the role of magnesium ions. Am. J. Cardiol. 1992; 7: 44C–49C.
3. Wester PO and Dyckner T. Intracellular electrolytes in cardiac failure. Acta Med. Scand. 1986, 207 (Suppl): 33 – 36.
4. Altura BM and Altura BT. Role of magnesium in patho-physiological processes and the clinical utility of magnesium ion selective electrodes. Scand J. Clin. Lab. Invest. 1996; 224 (Suppl.): 211 – 234.
5. Wester PO and Dyckner T. Magnesium and hypertension. J. Am Coll. Nutr. 1987; 6: 321 – 328.
6. Arsenian MA. Magnesium and cardiovascular diseases. Prog. Cardiovasc Dis. 1993; 35: 221 – 230.
7. Davies DL and Fraser R. Do diuretics cause magnesium deficiency? Br. Clin. Pharmacol. 1993; 36: 1 – 10.
8. Seller RH, Cangiano J and Kim KE. Digitalis toxicity and hypomagnesemia. Am. Heart J. 1970; 79: 57 – 68.
9. Olofsson BO, Nyhlin H and Wester PO. Beta-blockade or inhibition of angiotensin-converting enzyme does not affect intracellular magnesium or potassium. Curr. Ther Res. 1989; 46: 121 – 125.
10. Stevenson RN, Keywood C, Amadi AA, Davis JR and Patterson DLH. Angiotensin-converting enzyme inhibitors and magnesium conservation in patients with congestive heart failure. Br. Heart. J. 1991; 66: 19–21
11. Leier CV, Dei Cas L and Metra M. Clinical relevance and management of the major electrolyte abnormalities in congestive heart failure: Hyponatraemia, hypokalaemia, and hypomagnesemia. Am. Heart J, 1994; 128: 564 – 574.
12. Cohn JN and Rector TS. Prognosis of congestive heart failure and predictors of mortality. Am. J. Cardiol. 1986; 62: 25A – 30A.
13. Mckee PA, Castelli WP, McNamara PM and Kannel WB. The natural history of congestive heart failure: The Framingham study. N. Engl. J. Med. 1971; 285: 1441 – 1446.
14. Falase AO, Ayeni O, Sekoni GA and Odia OJ. Heart failure in Nigerian Hypertensives. Afr. J Med. Sci. 1983; 12: 7 – 15.
15. Ladipo GOA. Cardiac failure at Ahmadu Bello University Hospital. Nig. Med. J. 1978; 8: 96 – 99.
16. Spisak V. Serum and urinary concentrations of magnesium in patients with chronic heart failure. Vritrni Lekarstvi. 1996; 42 (10): 680 – 683.
17. Gottlieb SS, Baruch L, Kinkin ML, Bernstein J., Fisher ML and Packer M. Prognostic importance of the serum magnesium concentration in patients with CHF. J. Am Coll Cardiol. 1990; 16: 827 – 831.
18. Dorup I, Skajia K, Clausen T and Kjeldsen K. Reduced concentrations of potassium, magnesium and sodium-potassium pumps in human skeletal muscle during treatment with diuretic. Br. Med. J. 1988; 296: 455 – 458.
19. Beyenbach KW. Unresolved question of renal magnesium homeostasis. Magnesium 1986; 5: 234 – 247.
20. Shills ME. Experimental human magnesium depletion. Medicine. 1969; 48: 61 – 85.
21. Weinberger MH. Comparison of captopril and hydrochlorothiazide alone and in combination in mild to moderate essential hypertension. Br. J. Clin. Pharmacol 1982; 14: 1275 – 1315.
22. Bogdan M, Nortowicz E, Ukleja-Adamowicz M and Rozwodowska M. Serum and erythrocyte magnesium, potassium and sodium in patient with chronic congestive heart failure and after treatment with captopril. In Smetana R. ed., Advances in magnesium research. I, John Libbey Ltd. 1997; 66 – 70.
23. Broquist M, Dahlstrom U, Karlsson E and Larsson J. Muscle water and electrolytes in severe chronic congestive heart failure before and after treatment with enalapril. Eur. Heart J. 1992; 13 (2): 243 – 250.
24. Ryan MP. Diuretics and potassium/magnesium depletion: Directions for treatment. Am J Med. 1987; 82 (Suppl 3A): 38 – 47.
25. Hollifield JW. Magnesium depletion, diuretics and arrhythmias. Am J Med. 1987; 82 (Suppl 3A) 30 – 37.

Six patients had initial washout period of two weeks during which previous medications were discontinued. The remaining 39 patients were newly diagnosed and were not on any medications before recruitment into the study. 5 patients were treated with lisinopril (ACEI); 16 patients with frusemide (diuretic); 2 patients with digoxin; 14 were given a combination of lisinopril and frusemide; and 8 were given a combination of digoxin and frusemide. The control group consisted of forty-five healthy subjects (24 males and 21 females) of average age of 50 years (range 15 to 85 years), with routine examination results in the normal range.

Procedures and measurements

Peripheral venous blood was obtained from each subject at baseline and at the end of second and fourth week of follow-up. The sera were separated by centrifugation at 1000 rpm for 5 minutes and stored at -20 °C till seroanalysis. Aliquots of 24 hour urine samples collected in each subject at the end of baseline and end of second and fourth week were also stored at -20 °C. The magnesium concentration in the serum was determined by Atomic Absorption Spectrophotometer (AAS) (Model Buck Scientific Atomic Absorption/Emission Spectrophotometer) with direct dilution using acid Lanthanum oxide. Lanthanum Oxide and standard solution of magnesium used to calibrate the AAS were obtained from Sigma Scientific Company. All water used for solutions in this experiment was double distilled and double deionized. Magnesium concentration was expressed in mmol.L^{-1}. Reference values were assessed by determination of the mean values of serum and urinary magnesium in the 45 healthy control subject.

Statistics

The data was analysed using the WHO EPI-Info version 6 programme. All statistical tests were at the 5% probability level of significance ($P < 0.05$).

Results

The biochemical parameters at baseline were compared between cases and control as shown in Table 1. The serum magnesium concentration in CHF patients with a mean value of 0.82 ± 0.09 mmol.L^{-1}, though lower than that in controls, 0.93 ± 0.08 mmol.L^{-1}, did not reach statistical significance, $P > 0.1$. However, 13 (28.9%) CHF patients and 4(8.9%) control subjects had low serum magnesium. The urinary magnesium concentration was significantly higher in CHF patients, 3.39 ± 0.30 mmol.day^{-1} than in control subjects, who had 3.18 ± 0.19 mmol.day^{-1}, $P < 0.01$.

Table 1: Comparison of serum and urinary magnesium concentraton between CHF patients and control subjects at baseline.

	N	Mean	SD	*P* - value
Serum Mg^{2+} (mmol.L^{-1})				
CHF patients	45	0.82	0.09	>0.1
Controls	45	0.93	0.08	
Urinary Mg^{2+} (mmol.day^{-1})				
CHF patients	45	3.39	0.30	<0.01
Controls	45	3.18	0.19	

The effect of medication and duration of treatment on serum magnesium concentration is presented in figure 1.

With the exception of patients on lisinopril, serum magnesium concentration decreased significantly overtime in patients on other medications, $P < 0.05$. Patients on lisinopril had the highest concentration of serum magnesium, while those on digoxin and frusemide combination had the lowest concentration at each period of examination. The effect of medications on urinary excretion of magnesium is presented in figure 2. Excretion of magnesium was highest in those receiving digoxin and frusemide combination, and this was 4.25 ± 0.70mmol.day^{-1} while the lowest excretion of 3.16 ± 0.36 mmol.day^{-1} was found in those receiving lisinopril; $P < 0.05$.

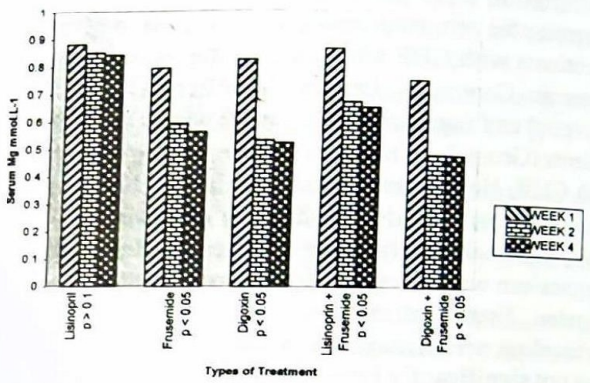

Fig. 1: The effect of treatment on serum magnesium

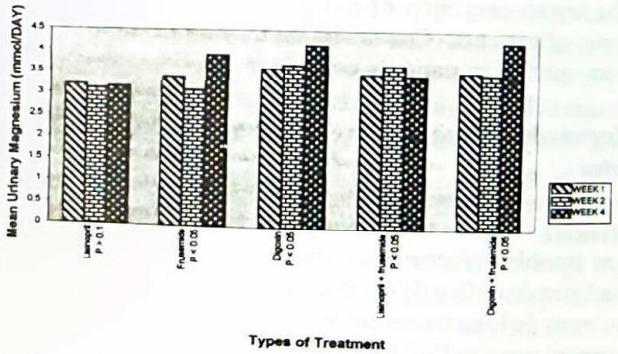

Fig. 2: The effect of treatment on urinary excretion of magnesium

Discussion

CHF is a relatively common medical problem in Nigeria [14,15] and its management is of increasing health importance because of the cost to health-care budget and the burden on the patient and relations. The condition is associated with high morbidity and mortality rates [13]. This study is in line with earlier observations [16] that patients in CHF had lower serum magnesium concentration than controls, and this may be related to secondary hyperaldosteronism that occurs in them. The prevalence rate of hypomagnesemia in CHF patients in this study was 28.9% which is higher than 9% and 20% [17,18] reported by other workers. Tissue magnesium depletion can be much higher with up to 50% prevalence rate quoted in some studies [3,18]. Hypomagnesemia indicates severe depletion and the high prevalence rate found in this study may be attributable to reasons which may not be obvious in this study. The urinary excretion of magnesium was significantly higher in CHF patients than controls, especially patients receiving frusemide and frusemide-digoxin combination. One of the major factors in magnesium conservation is