Third European Congress on Magnesium, Geneva

Amiloride in the Correction of Diuretic-Induced Intracellular Potassium and Magnesium Depletion

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Zusammenfassung

In diesen Versuch wurden dreizehn, wegen Hypertonie und/oder kongestiver Herzinsuffizienz langfristig (> 1 Jahr) mit einem Diuretikum behandelte Patienten (7 Männer und 6 Frauen) mit einem Durchschnittsalter von 62,6 ± 6,6 Jahren aufgenommen. Die frühere Diuretikumbehandlung wurde durch die Kombination von 5 mg Amilorid und 50 mg Hydrochlorothiazid (Moduretic®) ersetzt. Die intrazellulären Elektrolyte (K, Mg) wurden durch Muskelbiopsie ermittelt. Zu Beginn des Versuchs lagen niedrige mittlere intrazelluläre K- und Mg-Gehalte von je 40,7 ± 4,47 mmol/100 g FFDS (= Fat-Free Dry Solids/fettfreie Trockenfeststoffe) und 3,90 ± 0,67 mmol/100 g FFDS vor. Nach der Studie wurden die Elektrolytgehalte in den Muskeln wieder normal. Die intrazelluläre K-Konzentration betrug 45,4 ± 4,27 mmol/100 g FFDS ($p < 0,005$) und die entsprechende Mg-Konzentration 4,77 ± 0,52 mmol/100 g FFDS ($p < 0,005$).

Summary

13 patients (7 men and 6 women), mean age 62.6 ± 6.6 years, on long-term (> 1 year) diuretic treatment for arterial hypertension and/or congestive heart failure were included in the study and their previous diuretic treatment was replaced with a combination of 5 mg amiloride + 50 mg hydrochlorothiazide (Moduretic®). The intracellular electrolytes (K, Mg) were obtained by means of a muscle biopsy. At the onset of the study the intracellular mean K and mean Mg levels were low, 40.7 ± 4.47 mmol/100 g FFDS and Mg 3.90 ± 0.67 mmol/100 g FFDS respectively. After the study period the muscle electrolytes were normalized, the intracellular K level was 45.4 – 4.27 mmol/100 g FFDS ($p < 0.005$) and the intracellular Mg level was 4,77 ± 0.52 mmol/100 g FFDS ($p < 0.005$) respectively.

Résumé

Treize patients: (7 hommes et 6 femmes), âgés en moyenne de 62,6 ± 6,6 ans, recevant un traitement diurétique au long court (> 1 an) pour une hypertension artérielle et/ou une insuffisance cardiaque congestive, ont été inclus dans cette étude. Leur traitement diurétique préalable a été remplacé par l'association de 5 mg d'amiloride et de 50 mg d'hydrochlorothiazide (Moduretic®). Une biopsie musculaire a permis de doser les électrolytes intra-cellulaires (K, Mg). Au début de l'étude, les taux intra-cellulaires moyens de K et de Mg étaient faibles, respectivement 40,7 ± 4,47 mmol/100 g de FFDS (= Fat-Free Dry Solids/solides à l'états sec, dépourvus de lipides) et 3,90 ± 0,67 mmol/100 g de FFDS. Après l'étude les taux des électrolytes musculaires se sont normalisés, la concentration intra-cellulaire de K étant passée à 45,4 ± 4,27 mmol/100 g de FFDS ($p < 0,005$) et celle de Mg à 4,77 ± 0,52 mmol/100 g de FFDS ($p < 0,005$).

Introduction

Derangements of the electrolytes have been observed to alter the electrical stability and the ordered behaviour of the heart [1, 2]. Interest has focused largely on changes of the internal and external balance of potassium (K), but lately, disturbances of the magnesium (Mg) metabolism have attracted some attention [3]. Treatment with conventional diuretic agents constitutes one of the major causes of disturbances in the K and Mg balance. Thus, diuretics result in increased losses of these ions [4–6], losses that may ultimately lead to cellular deficiencies of K and Mg [7, 8]. In the case of a Mg deficiency [9] it is not possible to make up cellular K deficiency by K supplementation alone, since Mg is intimately involved in the active transport mechanism for K over the cell membrane [10].

In previous studies we have demonstrated that addition of spironolactone [11] to triamterene [12] and amiloride [13] to conventional diuretic treatment preserves the cellular K and Mg content in patients with arterial hypertension and/or congestive heart failure. The addition of magnesium aspartate to earlier diuretic therapy in the same type of patients caused a significant increase in skeletal muscle K and Mg compared to the control group [14]. *Hollifield* and *Slaton* observed a reduction in total body potassium and total plasma K concentration and a simultaneous increase in the incidence of ventricular premature beats (VPB) when the patients were exercised on a treatmill. There was a significant correlation between the change in the plasma K concentration and the change in incidence of ventricular ectopic beats [15].

The aim of the present study was to investigate skeletal muscle K and Mg in patients on long-term (> 1 year) diuretic treatment who had arterial hypertension and/or congestive heart failure when the earlier diuretic treatment was replaced by a combination of 5 mg amiloride + 50 mg hydrochlorothiazide (Moduretic®).

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Patients and methods

Originally 15 patients were included in the study, but 2 were excluded due to a laboratory failure. Thirteen participants (7 men and 6 women), mean age 62.6 ± 6.6 years, were studied over a period of six months. Ten patients had arterial hypertension (5 WHO 1, 5 WHO 2) and 3 had congestive heart failure (2 NYHA II and 1 NYHA III). Eleven patients were on bendroflumethiazide 2.5–5.0 mg/day and 2 were on furosemide 40–80 mg/day. The mean duration of earlier diuretic therapy was 50 ± 38 months. Two patients were on digitalis. Eleven patients out of 13 underwent a bicycle ergonometer test. At the onset of the study and at the end of the study six months later blood samples and skeletal muscle electrolytes were taken after an overnight fast and after a maximal bicycle ergonometer test had been performed with an ECG outprint. The incidence of ventricular ectopic beats at the highest load was recorded for each patient. Body weight, systolic and diastolic blood pressure were recorded. The diuretic medication was then switched to a combination of 50 mg hydrochlorothiazide -5 mg amiloride (Moduretic®).

The blood samples were analyzed for electrolytes by means of a conventional autoanalyzer technique (Na, K, Cl, CO_2, Ca, PO_4, creatine) or by atomic absorption spectroscopy (Mg). The technique for taking skeletal muscle biopsies has been described elsewhere [16]. The biopsies were analyzed for K, Mg, Na and Cl. The analytic and preanalytic procedures have been published previously [11].

Statistics

For comparison between the pre- and post-study values of a parameter, Student's t-test for paired observations was used. The mean values ± standard deviation are given, calculated by the formula for arithmetic means.

Results

There were no significant changes concerning mean body weight, mean systolic and diastolic blood pressure, plasma K or Mg during the six-month study period (tab. 1). Nor were there any significant changes in the mean plasma Na, Cl, PO_4, Ca or creatinine concentrations during the study, or any significant changes in the mean skeletal sodium and chloride levels at the end of the study compared to the onset of the study.

At the onset of the study the mean values for both skeletal muscle K and Mg was low, 40.7 ± 4.47 mmol/100 g FFDS and 3.90 ± 0.67 mmol/100 g FFDS respectively. After six months both the mean skeletal K and Mg were within normal limits, 45.4 ± 4.27 mmol/100 g FFDS and 4.77 ± 0.52 mmol/100 g FFDS respectively, and the increase in the mean values for K and Mg were significant ($p < 0.005$) compared to the levels obtained at the onset of the study (tab. 2). Only two patients had a significant incidence of ventricular ectopic beats at the onset of the study. All the others had only a minor incidence (0–3 ventricular ectopic beats/min). The two patients with a high incidence of ventricular ectopic beat at the onset of the study showed a sizeable reduction in such beats at the end of the study and an increase in their skeletal muscle K and Mg.

Tab. 1

	0	6 months
Body weight (mean ± SD) kg	75.2 ± 12.2	75.6 ± 13.6
Systolic and diastolic blood pressure (mean ± SD) mm Hg	153.9 ± 28.8 / 91.2 ± 11.4	145.8 ± 26.1 / 88.9 ± 7.7
p-K (mean ± SD) mmol/l	3.51 ± 0.45	3.35 ± 0.21
p-Mg (mean ± SD) mmol/l	0.74 ± 0.11	0.71 ± 0.06

Tab. 2: Skeletal Mg and K (mean ± SD) in mmol/100 g fatfree dry solids before and after the 6-month study period (normal values)

	0		6 months
K	40.7 ± 4.47	$p < 0.005$	45.4 ± 4.27
Mg	3.90 ± 0.67	$p < 0.005$	4.77 ± 0.52

Discussion

The patients at risk of developing potassium and magnesium depletion are often elderly patients on long-term diuretic treatment for hypertension and/or congestive heart failure. Among these patients there is a high frequency of secondary aldosteronism, due to heart disease, which is also increased by the diuretic treatment per se [17]. Other complicating factors which may increase the risk of magnesium and potassium deficiency among this group of patients, is concomitant medication with digitalis and a low dietary intake of magnesium.

The normal ratio between intra- and extracellular potassium is essential for the maintenance a normal membrane potential [18]. The normal extra- to intracellular potassium ratio is maintained by Na-K-ATPase

(the "sodium pump"), were sodium is actively pumped out of the cell and potassium into the cell. Magnesium is essential for the optimal activity of the "sodium pump" [10]. In states of magnesium deficiency the cell continuously loses potassium and sodium is accumulated on the inside of the cell, unless concomitant magnesium deficiency is corrected [9, 19]. Changes in the intra- to extracellular ratio will cause changes in the resting membrane potential, potassium conductance and repolarization, favoring the occurrence of serious cardiac disease [1].

Although magnesium, as mentioned above, is essential for the normal functioning of the "sodium pump", no experiment so far has demonstrated a decline in the Na-K-ATPase activity in magnesium deficiency. Another attractive theory is that magnesium deficiency creates a "leaky membrane", which causes loss of potassium from the cell and a concomitant accumulation of sodium on the inside of the cell. Digitalis is a well-known inhibitor of Na-K-ATPase, which may explain the additional risk associated with digitalis medication in patients with concomitant potassium and magnesium depletion. Digitalis even may cause increased losses of magnesium through a reduction of the tubular reabsorption of magnesium [20]. There may be a vicious circle, magnesium deficiency causes potassium deficiency and potassium depletion reduces tubular secretion of digoxin up to 50 % [21]. In congestive heart failure 35–45 % of all deaths occur suddenly, without any evidence of functional deterioration and these patients have a high frequency of ventricular arrhythmias [22]. A major reason for the high incidence of sudden death may be the heart disease per se. Other arrhythmogenic factors which may play a role are the activation of endocrine compensatory mechanisms; i.e. the activation of the renin-angiotensin system and increased levls of vasoconstrictor hormones such as noradrenaline, causing accumulation of sodium and increased losses of potassium and magnesium. Secondly the diuretic treatment induces a secondary aldosteronism, contributing to the disturbance of the potassium and magnesium balance favoring the occurrence of serious arrhythmias.

It seems rational to try to avoid diuretic-induced potassium and magnesium depletion. In previous studies we have reported that spironolactone [9], tiramterene [10], amiloride [11] or the addition of peroral magnesium aspartate hydrochloride [12] preserves cellular K and Mg. The present study seems to indicate that amiloride might have the ability to correct an existing intracellular depletion of K and Mg. Amiloride blocks the entry of potassium into the cell through reversible binding to the cell membrane. The reduced sodium input causes decreased transepithelial potential difference, leading to reduced potassium and hydrogen losses [23–25]. During the study period there was a tendency for seru potassium and magnesium levels to decrease. The reason may be that the amiloride dosage was not high enough to maintain an unchanged K and Mg serum level. The possibility that a miloride might cause a shift of K and Mg from extra- to intracellular space cannot be excluded.

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