The Effects of Antihypertensive Treatment with Hydrochlorothiazide on Lymphocyte and Serum Potassium and Magnesium Concentrations

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Zusammenfassung

17 Kranken mit milder und mäßiger, komplikationsloser essentieller Hypertonie wurde Hydrochlorothiazide (12.5–75.0 mg pro Tag) 12 Wochen lang gegeben. Man untersuchte den Kalium (K)- und Magnesium (Mg)-Gehalt in Lymphozyten (L) des Blutes und ihre Konzentration im Serum: zu Beginn, nach 2, 4, 8 und 12 Wochen der Behandlung. Der K-Gehalt in L ist angestiegen nach 12 Wochen ($p < 0.01$) und K-Konzentration im Serum ist nach 4 Wochen gesunken ($p < 0.05$) um nach 12 Wochen auf den Ausgangswert zurückzukommen. Der Mg-Gehalt in L und seine Konzentration im Blut zeigten keine signifikanten Veränderungen.

Summary

Hydrochlorothiazide in a dose of 12.5–75.0 mg/daily had been given to 17 patients with mild and moderate uncomplicated essential hypertension for 12 weeks. Lymphocyte potassium (K) and magnesium (Mg) and serum ion concentrations of these elements were measured initially and at 2, 4, 8 and 12 weeks of treatment. Lymphocyte K content increased at 12 weeks of treatment ($p < 0.01$). Serum K concentration decreased at 4 weeks ($p < 0.05$) approximating the initial level at 12 weeks. Changes in lymphocyte and serum Mg concentrations were not significant.

Résumé

Hydrochlorothiazide en dose de 12.5–75.0 mg par jour était donné à 17 malades avec l'hypertension artérielle primaire benigne et modérée non-compliquée par 12 semaines. Lymphocytaire potassium (L-K) et magnesium (L-Mg), les concentrations de ions du K et Mg dans le sérum ont été analysées avant et après 2, 4, 8, 12 semaines. L-K a été elevée après 12 semaines ($p < 0.01$) et sérum K diminuait après 4 semaines ($p < 0.05$) et après 12 semaines retournait à la valeur initiale. L-Mg et sérum Mg n'ont pas changées significativement.

Introduction

Pharmacological treatment of essential hypertension (EH) may produce changes in the electrolyte homeostasis of the organism. For instance hypokalemia and hypomagnesemia have been described in patients on diuretic therapy. Potassium (K) and magnesium (Mg) deficiency induced by diuretics is associated with a greater incidence of cardiac arrhythmias an sudden death [16, 17]. *Papademetriou* et al. [12], *Lief* et al. [7] and others [8, 9, 15] indicated that thiazide treatment did not produce an increase in cardiac arrhythmias in patients with uncomplicated EH.

The present study was undertaken to determine K and Mg content in the peripheral blood lymphocytes and blood serum in patients with uncomplicated essential hypertension undergoing a 12-week treatment with hydrochlorothiazide.

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Material and Methods

The study population was a group of 17 patients with uncomplicated EH selected for hydrochlorothiazide monotherapy in the Outpatient Hypertension Department. The patients studied were 9 women and 8 men in age 21 to 53 years ($\bar{x} = 33.3$). Mild hypertension was diagnosed in 10 and moderate in 7 patients. The patients had not been given hypotensive drugs before and their daily diets were not restricted with respect to sodium, potassium, magnesium and calcium content. Serum concentrations of the ions of these elements, as well as glucose, cholesterol levels and renal indices were normal.

The patients underwent a 12-week outpatient therapy with hydrochlorothiazide in a daily dose of 12.5–75.0 mg. Blood pressure measurements and laboratory tests were performed before the study and at 2, 4, 8 and 12 weeks of treatment. Hydrochlorothiazide therapy was initiated with a daily dose of 25.0 mg which was augmented to a maximal dose of 75.0 mg during subsequent check-up in case of failure or decreased to 12.5 mg daily. Laboratory tests included determinations of serum K and Mg ions as well as total K and Mg in lymphocytes. Blood samples were always drawn at 8.00 a.m. after 20–30 min rest. Lymphocytes were isolated from the peripheral blood by a modified *Boyum's* method [2]. Total K and Mg content in single lymphocytes was determined by electron probe X-ray microanalysis [10] described in the previous paper*. Potassium and magnesium concentration in blood serum was determined by

* Potassium and magnesium content in peripheral blood lymphocytes in patients with essential hypertension

flame photometry. Student's t-test was used to test for statistical significance of lymphocyte and serum K and Mg content. Mean values and standard errors have been displayed graphically. Statistical significance was taken as $p < 0.05$.

Results

In the 17 hypertensives on hydrochlorothiazide therapy lymphocyte K content gradually increased. It was $\bar{x} = 0.127 \pm 0.027$ % before therapy, $\bar{x} = 0.141 \pm 0.038$ % at 2 weeks, $\bar{x} = 0.146 \pm 0.038$% at 4 weeks, $\bar{x} = 0.148 \pm 0.051$ % at 8 weeks and $\bar{x} = 0.163 \pm 0.029$ % at 12 weeks. Lymphocyte K content at 12 weeks was significantly higher than that before therapy ($p < 0.01$) (Fig. 1).

Changes in lymphocyte K content were accompanied by a decrease in serum K concentration from an initial value $\bar{x} = 4.35 \pm 0.22$ mmol/l to $\bar{x} = 4.29 \pm 0.34$ mmol/l at 2 weeks and to $\bar{x} = 4.00 \pm 0.37$ mmol/l at 4 weeks of therapy. The latter change was significant at $p < 0.05$. At 8 and 12 weeks of therapy serum K content increased to the initial value $\bar{x} = 4.25 \pm 0.27$ mmol/l and $\bar{x} = 4.33 \pm 0.45$ mmol/l, respectively (Fig. 2).

During hydrochlorothiazide therapy lymphocyte and serum Mg content did not change significantly. Lymphocyte Mg content was $\bar{x} = 0.054 \pm 0.009$ % before treatment, $\bar{x} = 0.053 \pm 0.010$ % at 2 weeks, $\bar{x} = 0.053 \pm 0.008$ % at 4 weeks, $\bar{x} = 0.051 \pm 0.003$ % at 8 weeks and $\bar{x} = 0.060 \pm 0.013$ % at 12 weeks. Serum Mg concentration was $\bar{x} = 0.856 \pm 0.080$ mmol/l before therapy, $\bar{x} = 0.796 \pm 0.089$ mmol/l at 2 weeks, $\bar{x} = 0.847 \pm 0.086$ mmol/l at 4 weeks, $\bar{x} = 0.851 \pm 0.055$ mmol/l at 8 weeks and $\bar{x} = 0.884 \pm 0.078$ mmol/l at 12 weeks.

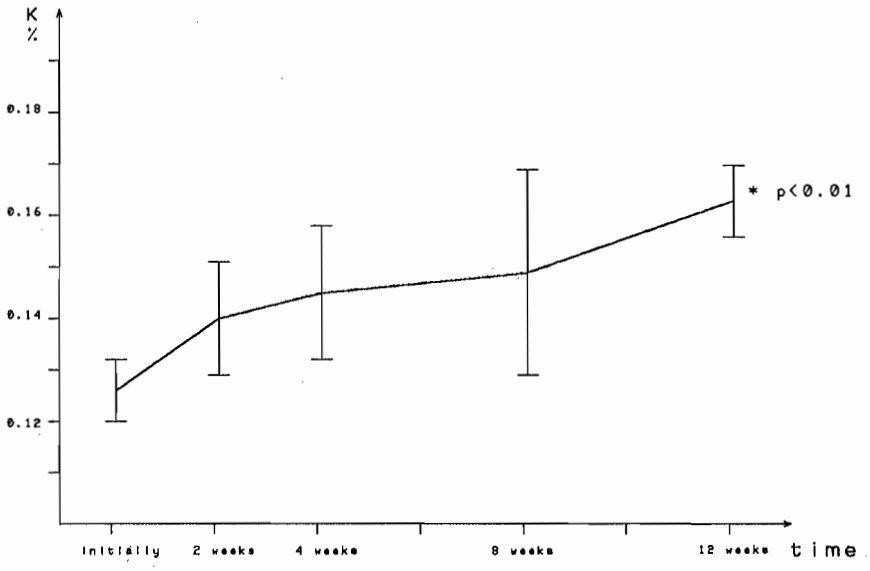

Fig. 1: Lymphocyte potassium content in patients with essential hypertension on hydrochlorothiazide treatment. (mean values and standard errors).

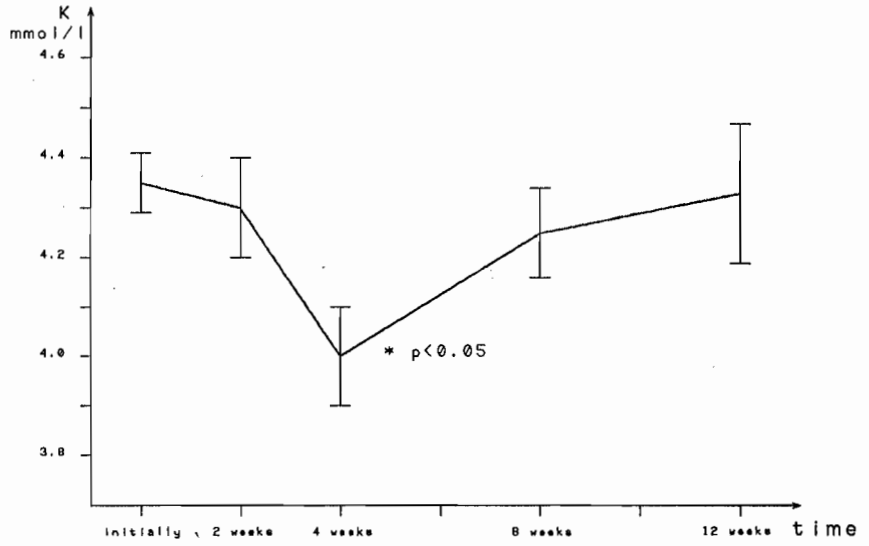

Fig. 2: Serum potassium concentration in patients with essential hypertension on hydrochlorothiazide treatment. (mean values and standard errors).

Discussion

Thiazide therapy initially leads to an excssive excretion of total body potassium of 5–10% (200–300 mEq), mainly from extracellular space [3, 11]. Potassium loss is most prominent within the first days of treatment decreasing in the course of thiazide therapy. After the initial changes the loss is in equilibrium with potassium supply. This is in accord with the observations of Wilkins et al.(18) who found no statistically significant changes in total body potassium after 12 months of thiazide treatment. The present study shows that serum K concentration during hydrochlorothiazide therapy decreased at 4 weeks, it however did not exceed hypokalemia threshold and at 12 weeks it returned to the initial value.

Changes in kalemia level in the hypertensives were accompanied by an increase in lymphocyte K content. This may be accounted for by the fact that thiazides influence a release of natriuretic hypothlamic hormone. Hypothalamic natriuretic factor is secreted as a result of an increase of serum sodium concentration and blood volume. It has "ouabain-like" properties. An excessive secretion, of hypothalamic natriuretic factor in patients with essential hypertension leads to an inhibition

of active K transport dependent on sodium-potassium pump in the cellular membrane [19]. Dysfunction of this pump increases passive efflux of K from the cell, accompanied by an increase in intracellular sodium and calcium levels resulting in an increased tone of the vascular smooth muscle cells which means an increase in the peripheral vascular resistance. Thiazides through their natriuretic action decrease the production of this hormone and in consequence improve the activity of the menbrane Na-K ATPase. The next step of thiazide action is not a reduction in circulating blood volume but a decrease in peripheral vascular resistance dependent on a decrease in intracellular sodium content and increase in intracellular K content [13, 14, 19]. Various authors report various levels of intracellular sodium and potassium in patients on thiazide therapy. *Ringel* et al. [14] ascribe this to a natriuretic hormone action on the activity of Na-K pump in the cellular membrane. This hormone causes the production of blood cells containing a larger amount of Na-K ATPase molecules in the cellular membrane. Thiazides in antihypertensive treatment reduce the production of natriuretic hormone. In consequence the hematopoetic system does not produce blood cells containing a large quantity of Na-K ATPase molecules. Due to a definite survival time of blood cells undergoing analysis and duration of pharmacotherapy intracellular Na and K levels may vary in different studies. During hydrochlorothiazide treatment lymphocyte and serum Mg content did not change significantly. Mg deficiency found in patients on diuretic treatment concerned mainly loop diuretics [4]. It is accounted for by the fact that about 60 % of Mg fraction filtered in the renal glomerules is absorbed in the descending limb of Henle loop. In contrast, thiazides acting in the proximal and distal tubule of the nephron to a considerably lesser degree cause urinary Mg excretion. It is in accord with clinical studies of *Kohvakka* at al. [5], *Kroenke* et al. [6], and *Araoye* et al. [1].

The present results schow that monitoring of the electrolyte changes, especially kalemia level during thiazide treatment in patients with uncomplicated EH permits us to abandon routine potassium supplementation or to use it in adequate doses in justified cases only.

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