Effect of Nifedipine on Serum Inorganic Phosphorus and Serum Magnesium in Hypertensive Patients

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Zusammenfassung

Die Wirkung von Nifepedin auf die Serumspiegel von anorganischem Phosphor und Magnesium wurde bei 54 Patienten mit essentieller arterieller Hypertonie untersucht. In 25 Fällen war der erhöhte Blutdruck mit Übergewicht verbunden. Bei 33 Patienten wurde eine Hypophosphatämie und bei 15 Patienten eine Hypomagnesiämie festgestellt. Es erwies sich, daß die orale Gabe von Nifedipin an 7–10 Tagen sowohl die Hypophosphatämie als auch die Hypomagnesiämie korrigierte. Wenn diese Variablen dagegen innerhalb der Normalgrenzen blieben, wurden keine Wirkungen festgestellt. Es wird vermutet, daß die Änderungen der Spiegel von anorganischem Phosphat bei Patienten mit erhöhtem Blutdruck und die Korrektur dieser Spiegel durch Nifedipin mit dem Kalziumstoffwechsel zusammenhängen. Die Erhöhung von Magnesium im Serum könnte, zumindest teilweise, die Abnahme des Blutdrucks nach der Behandlung mit Nifedipin erklären.

Summary

Effects of nifedipine upon serum levels of inorganic phosphorus and magnesium were studied in 54 patients with essential arterial hypertension; being associated with overweight in 25 cases. Hypophosphatemia was noted in 33 patients and hypomagnesemia in 15. Nifedipine given orally during 7-10 days was found to correct both hypophoshatemia and hypomagnesemia. On the other hand no effects were noticed when these variables were within normal limits. It is suggested that changes of serum Pi levels in hypertensive patients and their correction by nifedipine are related to calcium metabolism. Increase of serum magnesium could at least partially explain the decrease of blood pressure after treatment with nifedipine.

Resume

Les auteurs ont étudié les effets de la nifédipine sur les taux sériques de phosphore inorganique et de magnésium chez 54 patients souffrant d'hypertension artérielle essentielle, dont 25 patients atteints d'excès pondéral. Ils ont enregistré une hypophosphatémie chez 33 patients et une hypomagnésémie chez 15 patients. La nifédipine, administrée par voie orale pendant 7 à 10 jours, a permis de corriger ces deux carences mais n'a eu aucun effet sur ces paramètres lorsqu'ils se situaient dans les limites de la normale. On peut supposer que les variations des taux sériques de phosphore inorganique chez hypertendus et leur normalisation par la nifédipine sont liés au métabolisme calcique. L'augmentation de la magnésémie permet au moins d'expliquer en partie la baisse de la pression artérielle après traitement par la nifédipine.

Introduction

In a previous paper [28] we have shown that in patients with overweight and hypophosphatemia, propranolol led to an increase in the concentration of inorganic phosphorus (Pi) which could be connected to changes in carbohydrate metabolism. Actually beta blockers were found to reduce insulin secretion [11]. It could therefore be presumed that a lesser uptake of glucose and Pi into the cells would occur [28].

It was also found [30] that hypomagnesemia occurring in hypertensive patients is in 62.50% accompanied by hypophosphatemia.

There is increasing evidence that calcium is involved in the pathogenesis of essential arterial hypertension [10, 16, 23, 29]. Disturbances of calcium metabolism were also reported in animals experimentally rendered hypertensive [20]. Taking into the account the metabolic relationship between Ca and P and between Ca and Mg the effect of nifedipine, a calcium channel blocker, on serum levels of Pi and Mg was now investigated.

Material and Methods

54 patients with essential arterial hypertension stage II [WHO, 33] (35 females and 19 males) aged 53.90 ± 1.33 years) were treated with nifedipine 30–40 mg/day (Corinfar ®, VEB Arzneimittelwerk-DDR). In 25 subjects arterial hypertension was associated with overweight. Patients with acute diseases or suffering from diabetes mellitus, congestive heart failure, liver disease or impaired renal function were excluded from the study. No side effects were noted during therapy.

Variations affecting serum Mg and Pi concentrations during a time interval of 8 days were also investigated in 11 hypertensive patients who did not receive any therapy.

Serum Pi and serum Mg were determined colorimetrically using Merkotest standardized reagents. Normal values ranged 0.82 to 1.39 mmol/l for serum Pi and 0.84 to 1.00 mmol/l for Mg and the variation coeficients (v. c) calculated in 12 duplicates were

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vc = 7.35 % for Pi and vc = 4.27 % for Mg.
Statistical significance of the differences between mean values was calculated by paired difference analysis.

Results

Systolic and diastolic blood pressure decreased significantly during nifedipine therapy (Tab. 1). No significant correlation between the decrease of blood pressure and increase of serum Pi was noted.
33 hypertensive subjects were presenting Pi < 0.85 mmol/l, in 4 of them severe hypohosphatemia (Pi < 0.70 mmol/l) was noted. A significant rise of Pi ($p < 0.001$) occurred after 7–10 days of nifedipine therapy (Tab. 2).
In 21 patients normal values of Pi (mean initial value 1.08 ±0,02mmol/l) were found. Treatment with nifedipine did not change significantly serum Pi concentration in these patients (mean posttherapeutic values of Pi = 1.06 ± 0.06 mmol/l).
A different behaviour of serum Mg levels was noted in relation to the values recorded before nifedipine therapy. In hypertensive patients with initial serum Mg less than 0.85 mmol/l a significant increase ($p < 0.005$) of its level was noted after nifedipine (Fig. 1) while in hypertensive patients with serum Mg > 0,96 mmol/l, the level significantly ($p < 0,01$) decreased after nifedipine (Fig 2). No significant nifedipine induced changes of serum Mg were noted in patients with initial levels ranging 0.85 mmol/l to 0.95 mmol/l. There was no significant correlation between the increase of serum Pi and changes of serum Mg after therapy with this calcium antagonist.
In the 11 hypertensive patients who had received no therapy, serum Mg and Pi levels did not significantly vary from the initial base line (Mg = 0.88 mmol/l initially and 0.87 mmol/l after 8 days; Pi = 1.07 mmol/l initially and 1.07 mmol/l after 8 days.
In one patient hypophosphatemia (Pi < 0.68 mmol/l) was associated with frequent attacks of paroxysmal tachycardia. Nifedipine therapy led to an increase of serum Pi (0.90 mmol/l) as well as to a decrease in blood pressure to normal values while the tachycardic attacks subsided.

Discussion

Hypophosphatemia occurring in overweight hypertensive patients merely confirms our previously reported data [28].
The main mechanism involved in hypophosphatemia occuring in such patients seems to be the shift of phosphate from the extracellular into the intracellular compartment, induced by insulin, glucagon, catecholamine and androgens in order to phosphorilate various organic compounds [2,4,19]. Actually hypertensive patients and especially the obese ones quite often display hyperinsulinism and increades serum levels of cathecholamines [3, 7, 8, 27]. In such patients propranolol led to a correction of hypophosphatemia probably by reducing insulinemia and the subsequwnt penetration of Pi into the cells [14, 28].
It is questionable that the same mechanism could be attributed to the correction of hypophosphatemia by nifedipine. Actually while nifedipine reduced insulin secretion induced by glucose in vitro [26], it had no such effect in vivo [24].
Furthermore nifedipine leads to an increase of serum catecholamines [15, 18].
It is therfore more likely that the effect to nifedipine upon serum Pi

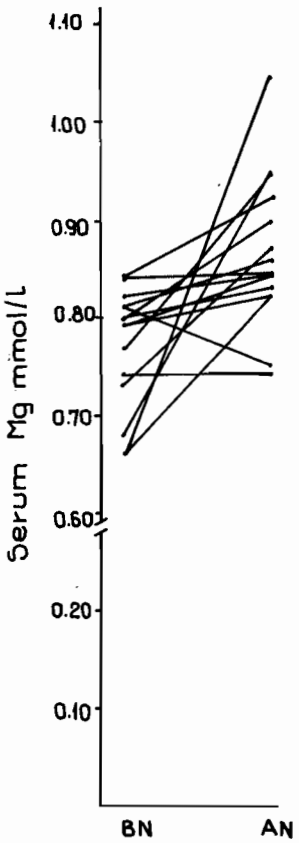

Fig. 1: Serum Mg levels before (BN) and after (AN) therapy with nifedipine in hypertensive patients in whom initial Mg concentrations were less than 0.85. mmol/l. Mean values increased from 0.77 mmol/l ± 0.01 (X ± SEM) to 0.86 mmol/l ± 0.02 ($p < 0.005$).

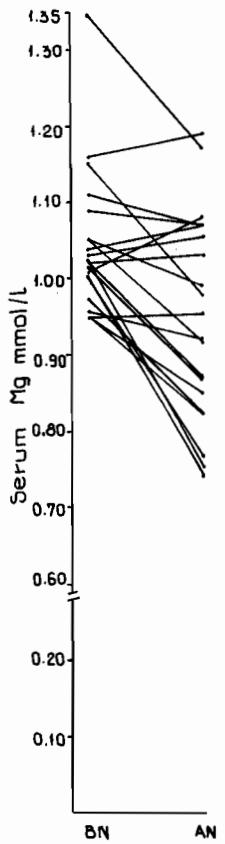

Fig. 2: Serum Mg before (BN) and after (AN) therapy with nifedipine in hypertensive patients in whom the initial Mg concentrations were higher than 0.96 mmol/l. Mean values decreased from 1.04 mmol/l ± 0.02 to 0.94 mmol/l ± 0.03 ($p < 0.01$).

Tab. 1: Age, body weight as well as systolic (SBP) and diastolic (DBP) blood pressure before (a) and after (b) nifedipine in patients with arterial hypertension (stage II). Mean ± SEM; number of investigated patients in brackets; **p > 0.001 (calculated by paired difference analysis) Pi – inorganic phosphorus.

Group	Age (years)	Body weight (kg) a	Body weight (kg) b	SBP (mm Hg) a	SBP (mm Hg) b	DBP (mm Hg) a	DBP (mm Hg) b
All hypertensive patients (54)	53.90 ±1.33	73.43 ±1.82	73.81 ±1.91	203.00 ±3.00	154.90** ±5.30	112.60 ±1.70	90.80** ±1.70
Hypertensive patients with Pi < 0.85 mmol/l (33)	53.40 ±1.58	74.00 ±2.20	73.74 ±2.13	203.30 ±2.80	151.20** ±5.50	113.60 ±2.50	89.10** ±2.50
Hypertensive patients with Pi > 0.85 mmol/l (21)	54.75 ±2.43	72.50 ±3.25	72.40 ±2.95	202.50 ±5.20	161.00** ±5.10	111.00 ±2.30	93.80** ±2.40

should be related to changes in Ca metabolism. In some hypertensive patients hypophosphatemia was discussed to be, at least partially, related to an increase in parathormone secretion, stimulated by low levels of serum calcium [13, 23] or after thiazide therapy [2,23]. On the other hand nifedipine was reported to decrease intracellular calcium concentration [9, 12, 32] by reducing calcium influx into the cell [5], and pro bably leads to an increase of serum calcium levels. This effect was obtained with folodipine, a structural analog of nifedipine [12]. The increase of serum calcium concentration could thus depress the secretion of parathormone and increase serum Pi. Accelerated turnover of membrane phosphoinositides, possibly involved in pathogenesis of arterial hypertension [21], could represent another mechanism for abnormalities in serum Pi. A significant negative correlation between mean blood pressure and serum Pi was reported in healthy subjects [13] and previous investigations demonstrated a significantly positive correlation between the increase in serum Pi and decrease of arterial pressure after propranolol in hypertensive subjects [28].

Correction of hypophosphatemia is very important in hypertensive patients because it restores cardiac performance [22,31]. Actually severe hypophosphatemia may lead to a depletion o f ATP and 2,3 DPG in erytrocytes, a process which would impair the delivery of oxygen to the tissues [17, 31].

Tab. 2: Serum inorganic phosphorus (PI) and magnesium (Mg) in hypertensive patients before (a) and after (b) therapy with nifedipine. Mean ± SEM; number of patients in brackets. Statistical significance calculated by paired difference analysis: * p 0.0l; ** p < 0.001.

Group	Pi (mmol/l) a	Pi (mmol/l) b	Mg (mmol/l) a	Mg (mmol/l) b
All hypertensive patients	0.89 ±0.01 (54)	0.97* ±0.02 (54)	0.92 ±0.02 (52)	0.92 ±0.02 (52)
Hypertensive patients with Pi < 0.85 mmol/l	0.80 ±0.01 (33)	0.91** ±0.02 (33)	0.92 ±0.02 (32)	0.93 ±0.02 (32)
Hypertensive patients with Pi > 0.85 mmol/l	1.08 ±0.02 (21)	1.06 ±0.06 (21)	0.92 ±0.03 (20)	0.91 ±0.03 (20)

It should be mentioned that a decrease of serum Mg after felodipine was also reported [12]. It is known that Mg is a natural inhibitor of calcium in smooth muscle and myocardium [6] and hypomagnesemia favors the vasospasms and the increase of arterial pressure [1, 25].

We have, so far, no obvious explanation for the normalizing effect of nifedipine therapy upon serum magnesium level. One may nevertheless suggest that such changes like those affecting Pi could be somehow related to shifts of calcium between intracellular and extracellular compartments.

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