Resistance to the Calcemic Action of Parathormone in Magnesium Deficiency

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Zusammenfassung

Bei fünf Patienten, die infolge eines Magnesiummangels zu niedrige Magnesium- und Kalziumspiegel aufwiesen, wurde das Reaktionsvermögen der Knochen auf Parathormon untersucht. Dazu diente die Reaktion der Kalziumwerte im Plasma auf synthetisch hergestelltes humanes Parathormon.
Bei zwei der Patienten mit leichter Hypomagnesiämie reagierte der Kalziumspiegel normal, während die anderen drei Patienten mit mäßiger Hypomagnesiämie für das Parathormon unempfänglich waren.

Summary

The plasma calcium response to synthetic human parathormone was used to assess the ability of bone to respond to parathormone in five patients with hypomagnesemic hypocalcemia secondary to Mg deficiency. Two patients with mild hypomagnesemia had a normal calcemic response. Three patients with moderate hypomagnesemia were refractory to parathormone.

Résumé

On a utilisé la réponse calcique plasmatique vis à vis de la parathormone humaine synthétisée pour déterminer l'aptitude de l'os à réagir à la parathormone, chez cinq patients attaints d'hypomagnésémie hypocalcémique cosécutive à une carence en magnésium.
Deux patients souffrant d'hypomagnésémie légère ont présenté une réponse calcémique normale, alors que trois patients souffrant d'hypomagnésémie modérée ont été réfractaires à la parathormone.

Introduction

The definitive diagnosis of pseudohypoparathyroidism must be established through application of laboratory tests that reflect the underlying pathophysiology of the disorder, namely, resistance to the biological actions of parathormone. Accordingly, defective responsiveness of the kidney and bone to parathormone must be documented.
The plasma calcium response to synthetic human parathormone (1-34) peptide was used to assess the ability of bone to respond to parathormone in five patients with hypomagnesemia-induced "pseudohypoparathyroidism". Two of the patients with mild hypomagnesemia had a normal calcemic response, while the three patients with moderate hypomagnesemia were refractory to parathormone.

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Patients and Methods

Five patients with intestinal malabsorption, hypomagnesemia and hypoalcemia (both corrected for hypoalbuminemia) where chosen for the study. Radiographic bone changes, bone pain and osteomalacia were not found in these patients. A patient with idiopathic hypoparathyroidism served as control. All patients gave their informed consent.
Each patient received 25 μg synthetic human parathormone (1-34) peptide i.v. daily for 4 days. The infusion was completed within 15 min. Blood samples for calcium, Mg and albumin were taken before the infusion and 2 hours after its termination [1]. The patients had endogenous creatinine clearance within the normal range. Total serum calcium and Mg were measured by AAS and corrected for hypoalbuminemia [2].
During the first day of Mg replenishment with $MgSO_4 \cdot 7H_2O$, 1.0 mEq of Mg per kg body weight was given parenterally. Replenishment was continued for 4 more days with doses one half of that of the first day [3].

Results

The control patient (idiopathic hypoparathyroidism) with a normal serum Mg of 2.0 mg/dl (normal range 1.68 – 2.4 mg/dl) had a baseline plasma calcium of 6.5 mg/dl which rose on the fourth day of PTH administration to a level of 9.7 mg/dl (normal range 8.5 - 11 mg/dl). Two of the patients with mild hypomagnesemia, 1.44 and 1.20 mg/dl, rose their decreased plasma calcium levels to 10.22 and 10.00 mg/dl. The other three patients with moderate hypomagnesemia 1.1, 0.97 and 0.87 mg/dl rose their decreased plasma calcium levels only to within 1 mg/dl above their baseline values (fig. 1). Mg replenishment normalized both plasma calcium and Mg levels.

Discussion

Hypomagnesemia, Mg $<$ 1.2 mEq/l is present in 23 % of patients with hypocalcemia, calcium corrected for hypoalbuminemia $<$ 8.6 mg/dl (4,5).
In experimental Mg deficiency in man, urinary calcium excretion falls rapidly despite a constant calcium intake. Mg

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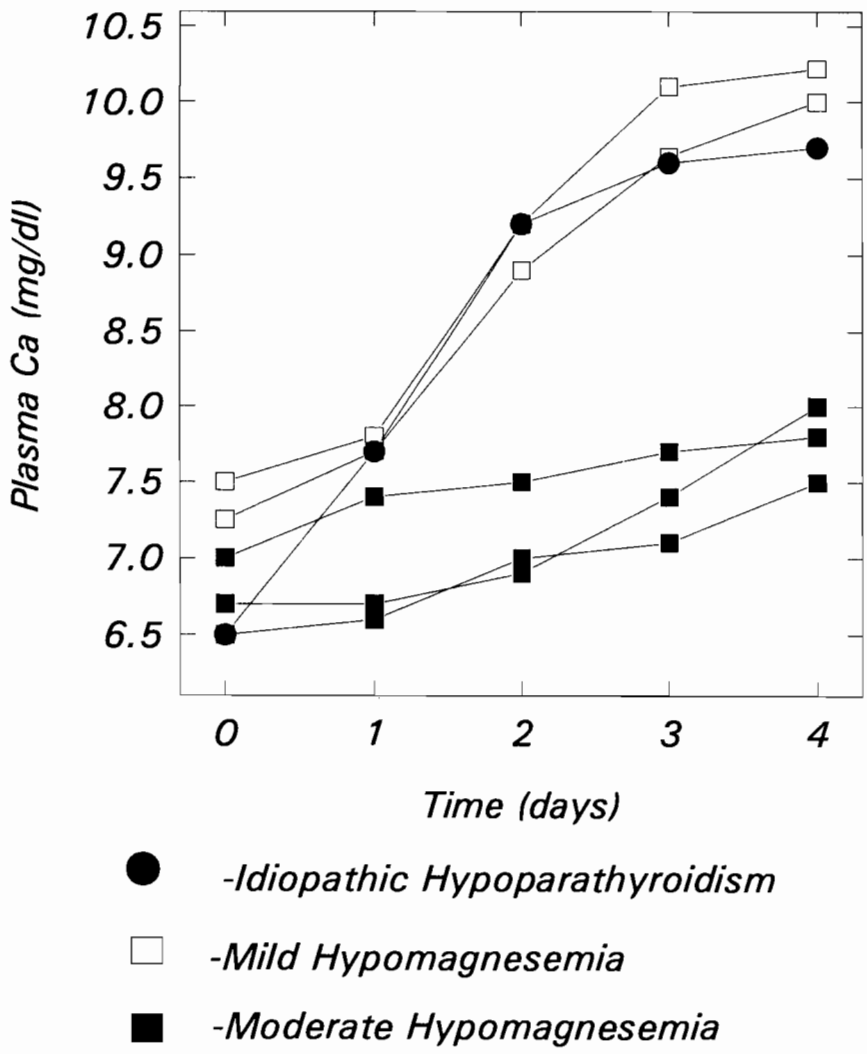

Fig. 1

deficient patients have a reduced urinary calcium excretion, normal bone calcium concentration and a positive calcium balance. During Mg depletion intestinal calcium absorption is normal and there is no increased fecal calcium. Bone biopsies have been reported from two Mg deficient patients but no abnormalities have been found. Most patients have either low or "inappropriately normal" serum parathormone levls in the face of hypocalcemia. The hypocalcemia is refractory to treatment with calcium and vitamin D but is correctable by replenishment of Mg alone [6]. In Mg deficiency states the regulatory mechanisms that maintain serum calcium in the normal range are impaired.

In most patients with hypomagnesemic hypocalcemia, concentrations of 1,25 $(OH)_2D$ are at the lower limit of normal or in the slightly subnormal range [7]. Hypocalcitoninemia could not be demonstrated in human Mg deficiency [8].

The most common cause of hypomagnesemic hypocalcemia is small bowel disease, including shortend small bowel, coeliac disease, malabsorption due to other causes, radiation enteritis, severe enteritis due to other causes, or rarely a primary defect of intestinal Mg absorption. Hypomagnesemic hypocalcemia may occur in alcoholism due to renal Mg loss in the presence of inadequate Mg intake. Excessive renal Mg loss may lead to hypomagnesemic hypocalcemia following therapy with high doses of gentamicin, cisplatinum, pentamidine, as well as in diabetes mellitus and in primary renal Mg wasting. Hypomagnesemic hypocalcemia has also been described in chronic parenteral therapy and anorexia nervosa [9].

Patients with intestinal malabsorption often have radiographic bone changes, bone pain, osteomalacia and minor – if any – hypocalcemia. However, in a few patients with malabsorption, very low serum calcium with tetany may develop in the absence of radiographic or symptomatic bone disease, suggesting that secondary hyperparathyroidism has failed to mobilize bone to increase serum calcium. *Muldowney* et al. [10] noted that in 5 of 9 patients with hypomagnesemia and hypocalcemia due to intestinal malabsorption parathyroid hormone increased phosphaturia but failed to raise serum calcium until Mg was replenished. Thus Mg deficiency in intestinal malabsorption could be regarded as protective, since secondary hyperparathyroidism failed to produce resorption of bone and calcium from the skeleton.

Parathyroid extract had neither a calcemic nor a phosphaturic effect in 8 alcoholic patients who were both hypocalcemic and hypomagnesemic but both defects disappeared following correction of Mg depletion. The finding suggested end-organ resistance to the effect of parathormone [11]. Why parathyroid hormone was effective on the kidney and caused phosphaturia in the patients with malabsorption and not in the alcoholic patients is not known.

In spite of the fact that some studies suggest that the calcemic response to parathormone may be more a function of plasma concentration of 1,25 $(OH)_2D$ than that of the innate responsiveness of bone to parathormone [12], it has been found that in hypomagnesemic hypocalcemia, the rise in serum calcium during Mg replenishment occurs before and independently of increases in 1,25 $(OH)_2D$ values [7].

Biochemically, resistance to the actions of exogenous parathormone was explained by a failure of parathormone activated adenylate cyclase in bone and kidney to produce sufficient amounts of cAMP in the presence of Mg depletion, Mg-ATP being the substrate of this enzyme. However, other meta-

bolic reactions dependent on membrane-bound adenylate cyclase, such as the surge of cAMP in plasma in response to glucagon, or the rise of cortisol, LH or TSH in serum in response to ACTH, Gn-RH or TSH respectively, remained unimpaired. These divergent effects of Mg deficiency on adenylate cyclase activity in different organs were explained by higher Mg requirements of the adenylate cyclase in parathyroids, kidney and bone as compared to other tissues in various animal species. This, however, has not been demonstrated in tissues in a single animal species that characteristically develops hypocalcemia during Mg depletion [9]. *Allgrove* et al. [13] found a singificant positive correlation between serum Mg and parathormone at the time of presentation. Moderate hypomagnesemia was associated with raised parathormone values, as Mg depletion became more profound parathormone was lower and it was undetectable when serum Mg was as low as 0.4 mEq/l. No such relationship existed between parathormone and serum calcium. They also found, that end-organ resistance was associated with mild degrees of Mg deficiency and no end-organ resistance when parathormone was low or undetectable as a result of severe Mg deficiency. They suggested therefore, that resistance to parathormone in Mg depletion is likely to be due to high concentrations of circulating parathormone.

In our investigation we found no bone resistance in mild hypomagnesemia but pronounced bone resistance to parathormone in moderate hypomagnesemia.

The hypocalcemia of Mg deficiency has also been explained by altered equilibrium between calcium in extracellular fluid and in bone. Experimental work has indicated that most Mg in bone can be displaced relatively easily and selectively implying that Mg is loosely associated with the crystal surfaces. *Pack* and *Diller* using a kinetic approach to investigate the interaction of Mg and other ions with bone surfaces concluded that much of the Mg in bone is present in the crystal hydration layer, a view put forward by *Neuman* for synthetic systems. In fresh human bone about 30% of the Mg is readily exchangeable equilibrating easily with serum and consistent with a hydration layer location. *Neuman* and *Neuman* postulated that Mg ion may exchange for calcium on the bone surface [14].

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