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Increase in serum magnesium level in haemodialysis patients receiving sevelamer hydrochloride

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Abstract. *Background*: Clinical studies have shown that sevelamer hydrochloride improves lipid profiles and attenuates the progression of the cardiovascular calcifications in haemodialysis patients. It is known that both of these properties are associated with increased magnesium levels. The effect of sevelamer on serum magnesium level is not well documented. The aim of this study was to determine the effects of sevelamer treatment on serum magnesium in haemodialysis patients and to assess the association of magnesium levels with lipid profiles and intact parathyroid hormone (iPTH). *Methods*: Phosphate binders were discontinued during a two week washout period. Forty-seven patients, whose serum phosphate was greater than 6.0 mg/dl at the end of washout, received sevelamer hydrochloride for eight weeks. The patients were then washed off sevelamer for another two weeks. *Results*: Mean serum phosphorus concentration declined from 7.5 ± 1.3 to 6.4 ± 1.2 mg/dl ($P < 0.001$), mean serum magnesium levels increased from 2.75 ± 0.35 to 2.90 ± 0.41 mg/dl ($P < 0.001$) and median serum iPTH levels decreased from 297 to 213 pg/ml ($P = 0.001$) during the eight weeks of sevelamer treatment. After the two week post-treatment washout phosphorus levels increased to 7.3 ± 1.3 mg/dl ($P < 0.001$), magnesium levels were reduced to 2.77 ± 0.39 mg/dl ($P < 0.001$) and iPTH levels increased to 240 pg/ml ($P = 0.012$). No change was observed in serum calcium levels during the sevelamer treatment period and the subsequent washout period. The mean decline in total and low density lipoprotein (LDL) cholesterol during sevelamer treatment was 16.3% and 28.3% ($P < 0.001$), respectively. The mean increase in high density lipoprotein (HDL) cholesterol and in apolipoprotein A1 was 2.9 ± 5.8 mg/dl ($P = 0.004$) and 6.8 ± 11.1 mg/dl ($P = 0.001$), respectively. Multivariate analysis showed that the rise in serum magnesium concentration significantly correlated with reductions in iPTH levels ($r = -0.40$, $P = 0.016$), but did not have any significant correlation with the changes in lipid profiles. *Conclusions*: Our findings indicate that patients on haemodialysis receiving sevelamer have a significant increase in serum magnesium concentrations. This increase in serum magnesium is associated with reduction in iPTH levels. The changes in lipid profiles of these patients however are not related to changes in serum magnesium levels.

Key words: Haemodialysis, Lipids, Magnesium, Parathyroid hormone, Sevelamer hydrochloride

Introduction

Sevelamer hydrochloride is a calcium-, aluminum- and metal-free phosphate binder that significantly lowers the serum phosphorus levels in haemodialysis patients with minimal effects on calcium levels. Chemically, sevelamer is a cationic hydrogel of cross linked, hydrophilic, polyallylamine polymer that is completely resistant to digestive degradation and is not absorbed from the gastrointestinal tract.

Clinical studies in haemodialysis patients have shown that in addition to its primary function as a phosphate binder, sevelamer significantly reduces iPTH and LDL cholesterol [1], increases HDL cholesterol [2], and plays a role in decreasing the progression of coronary and aortic calcifications [3]. Sevelamer binds and sequesters bile acids and this may explain its blood cholesterol lowering effects. Moreover, reduced calcium intake, fewer episodes of hypercalcemia, improved control of iPTH, and other mechanisms related to lipid lowering effects of sevelamer may be responsible for the attenuation of arterial calcifications. Nevertheless, the exact mechanisms for these properties of sevelamer have not been fully established.

It is also known that the above properties are associated with increased magnesium levels. Lipid profiles change in a favorable direction with magnesium supplementation, in patients with ischemic heart disease [4], type II diabetes [5], renal insufficiency [6] and nondiabetic renal transplant recipients [7]. It has also been shown that increased serum magnesium concentration suppresses PTH secretion [8]. In addition, magnesium plays a fundamental role in the pathophysiology of arterial calcifications and hypermagnesemia may retard the development of arterial calcifications in end stage renal disease patients [9].

Therefore, one could assume that if sevelamer raises magnesium levels, this effect might contribute to a certain degree to its favorable effect on iPTH as well as on both arterial calcifications and lipid profiles.

The current study was undertaken to determine the effects of sevelamer hydrochloride treatment on serum magnesium levels in haemodialysis patients and to assess the association of serum magnesium with lipid profiles and iPTH levels.

Subjects and methods

Fifty-five patients, who were treated in the dialysis unit of the ''Papageorgiou'' General Hospital for a minimum of three months with haemodialysis three times per week, enrolled in the study. The protocol of the study was approved by the Institutional Scientific Board of the ''Papageorgiou'' General Hospital, Thessaloniki, Greece. Inclusion criteria included age 18 years or above, stable dosage of calcium or aluminum containing phosphate binders and no vitamin D metabolite replacement therapy, for at least one month prior to the enrollment in the study. Exclusion criteria included the presence of a clinically serious medical condition, total parathyroidectomy and active malignancy. None of the patients was taking lipid lowering medications. Over the course of the study, patients were prohibited from consuming antacids containing aluminum or magnesium and were asked to avoid intentional changes in their diet. All patients were receiving conventional dialysis for 210–240 minutes on each session with dialysate calcium and magnesium concentration 6.64 and 1.08 mg/dl, respectively. During the study period, the dialysis regimen, as well as the whole medication profile remained unchanged.

All patients were screened and then entered a two week washout phase during which all calcium- or aluminum containing phosphate binders were discontinued. Patients were eligible to receive sevelamer hydrochloride for eight weeks if serum phosphate was greater than 6.0 mg/dl at the end of washout. At the end of the eight week treatment period, patients were washed off sevelamer for two weeks to ensure that all the possible alterations were due to sevelamer treatment.

Sevelamer was supplied as hard gelatin capsules containing 403 mg sevelamer hydrochloride. The starting medication dose was determined by the initial degree of hyperphosphatemia and ranged from 2.4 to 4.8 g per day, taken with meals (Table 1). At the end of each of three subsequent two week periods, dosage was increased by 0.4 g per meal as needed to achieve adequate control of serum phosphorus (≤6 mg/dl).

Blood samples were collected each week before the mid-week dialysis session, and the timing was uniform within each subject. Measurements of serum phosphorus, calcium, magnesium, alkaline phosphatase, total cholesterol and LDL cholesterol levels were performed on an OLYMPUS AU-400

Table 1. Serum phosphorus at the end of washout and starting sevelamer doses for patients on haemodialysis

Starting sevelamer doses (g/day)	Washout serum phosphorus (mg/dl)	Number of patients
2.4	>6.0 – <7.0	20
3.6	≥7.0 – ≤8.5	11
4.8	>8.5	7

clinical chemistry analyzer (Olympus, Hamburg, Germany). The reagents for the measurement of serum phosphorus, calcium, magnesium, alkaline phosphatase, total cholesterol and triglycerides were from Olympus, Hamburg, Germany. Inorganic phosphorus was measured by the phosphomolybdate method, magnesium by the xylidylblue method, calcium by the arsenazo III method, alkaline phosphatase by the *p*-nitrophenylphosphate method, total cholesterol by the CHOD-PAP method, triglycerides by the GPO-PAP method and HDL cholesterol by an immunoinhibition method. LDL cholesterol was determined by the indirect method from the concentrations of total cholesterol triglycerides and HDL cholesterol. Lipoprotein A, apolipoprotein A1 and B were measured on a Beckman Array 360 system by nephelometry (Beckman Coulter, Krefeld, Germany). The reagents for lipoprotein A, apolipoprotein A1 and B were from Beckman Coulter, Krefeld, Germany. Serum iPTH (total PTH) was measured by the solid phase two-site chemiluminescent enzyme-labeled immunometric method in the immulite analyzer, using reagents of DPC Diagnostic Products (DPC, Los Angeles, CA, USA).

Statistical analysis

Serum concentrations expressed as mean values ± SD (or ± SE if it is indicated) or median when the data were highly skewed, were compared using Student's *t*-test. Univariate and multivariate linear regression was used to examine the possible effect of changes in calcium, phosphorus and the mean dose of sevelamer on serum magnesium and of changes in calcium, phosphorus, magnesium and the mean dose of sevelamer on iPTH. Pearson correlation was used to assess the association between changes in serum magnesium and in lipid values. All statistical analyses were based on two-tailed hypothesis tests, with a significance level of $P < 0.05$. Statistical analyses were conducted using the SPSS 10.0 statistical software for Windows (SPSS Inc, Chicago, IL).

Results

Fifty-five patients entered the first washout period; 47 of them had serum phosphorus greater than 6.0 mg/dl at the end of washout and qualified for sevelamer treatment. Thirty-eight patients completed the study. Eight patients dropped out due to an adverse event (3 due to vomiting, 3 due to abdominal pain, 1 due to dyspnea and 1 due to diarrhea) and one patient died of a cerebrovascular accident. Table 2 shows the baseline characteristics of the patient population. The majority of the patients (32 from 38) had a urine output of less than 100 ml per day.

The mean starting daily dose of sevelamer was 3.2 g, whereas the mean daily dose at the end of the eight week treatment period was 3.8 g. The average dose during the eight week treatment period was 3.5 g per day.

During the pre-treatment washout period the serum phosphorus levels rose from a baseline of 6.3 ± 1.3 to 7.5 ± 1.3 mg/dl ($P < 0.001$) and the serum calcium levels decreased from 9.3 ± 0.9 to 9.1 ± 0.8 mg/dl ($P = 0.034$). After sevelamer was initiated, serum phosphorus levels declined to a mean of 6.4 ± 1.2 mg/dl ($P < 0.001$) at the end of the treatment period. As expected, after the post treatment washout, mean serum phosphorus significantly increased to 7.3 ± 1.3 mg/dl ($P < 0.001$). No change was observed in serum calcium levels during the sevelamer treatment period and the subsequent washout period.

Changes in serum phosphorus were paralleled by changes in serum iPTH levels. Median iPTH rose during the pre treatment washout period from

Table 2. Patient characteristics

Characteristics	Patients entered the study (*n* 47)	Patients completed the study (*n* 38)
Age (yr)	60.0 ± 2.2	60.5 ± 12.0
Gender (male:female)	21:26	18:20
Weight (kg)	67.6 ± 12.0	68.1 ± 2.2
Duration on dialysis (mo)	34.1 ± 20.8	34.5 ± 22.9
Primary renal disease (nephritis:diabetes: hypertension:other)	14:10:10:13	13:7:6:12
Previous phosphate binder		
Calcium carbonate alone	25	21
Aluminum alone	12	8
Calcium carbonate + aluminum	10	9

Table 3. Factors associated with the proportional change of iPTH

Factors	Univariate analysis		Multivariate analysis	
	r	*P*	*r*	*P*
Pc* of serum calcium	−0.35	0.032	−0.33	0.050
Pc* of serum magnesium	−0.35	0.030	−0.40	0.016
Pc* of serum phosphorus	0.17	0.301	0.18	0.282

*The proportional change from the end of the initial washout period to the end of the treatment period.

193 to 297 pg/ml ($P = 0.008$). Upon initiation of sevelamer treatment, median iPTH declined to 213 pg/ml by the end of the treatment period ($P = 0.001$). During the second washout period, median serum iPTH increased to 240 pg/ml ($P = 0.012$). The univariate and multivariate associations of the proportional change of iPTH with changes in calcium, phosphorus and magnesium are illustrated in Table 3. There was a significant association between the proportional change in serum iPTH and the change in both magnesium (Figure 1) and calcium levels.

The primary outcome was the change in serum magnesium concentration in relation to treatment with sevelamer. Seventy three percent ($n = 27$) of the study patients had serum magnesium levels higher than 2.5 mg/dl (normal range: 1.9–2.5 mg/dl) at the beginning of the treatment period and this percentage increased to 84% ($n = 32$) eight weeks later. Mean serum magnesium levels on calcium and/or aluminum containing phosphate binders were 2.71 ± 0.34 mg/dl. With cessation of phosphate binder therapy during the pre treatment washout period, mean serum magnesium levels remained unchanged. Following sevelamer hydrochloride treatment, serum magnesium levels rose to a mean of 2.90 ± 0.41 mg/dl at the end of the treatment period ($P < 0.001$). Two weeks after sevelamer treatment was discontinued, serum magnesium declined to 2.77 ± 0.39 mg/dl ($P < 0.001$) (Figure 2). There was no significant correlation between the change in serum magnesium during sevelamer treatment and mean sevelamer dose, and changes in calcium or phosphorus levels.

Significant changes in lipid profiles were also noted. Serum total cholesterol decreased from a baseline of 209.4 ± 57.5 mg/dl at the end of the first washout, to 173.1 ± 47.5 mg/dl at the end of sevelamer treatment ($P < 0.001$), representing a decline of 16.3%. LDL cholesterol decreased from 136.6 ± 51.4 g/dl at baseline to 94.6 ± 34.1 mg/dl at the end of sevelamer treatment ($P < 0.001$). The mean decrease in LDL cholesterol of 41.9 ± 35.8 mg/dl represented a decline of 28.3%. The mean increase in HDL cholesterol and in apolipoprotein A1 was 2.9 ± 5.8 mg/dl ($P < 0.004$) and 6.8 ± 11.1 mg/dl ($P < 0.001$), corresponding to a proportional increase of 8.9 and of 6.7% from baseline respectively. Triglyceride and apolipoprotein B levels were not significantly altered, with a mean change of 17.8 and of −5.6 mg/dl respectively. The ratio between apolipoprotein A1 and apolipoprotein B was significantly affected, from

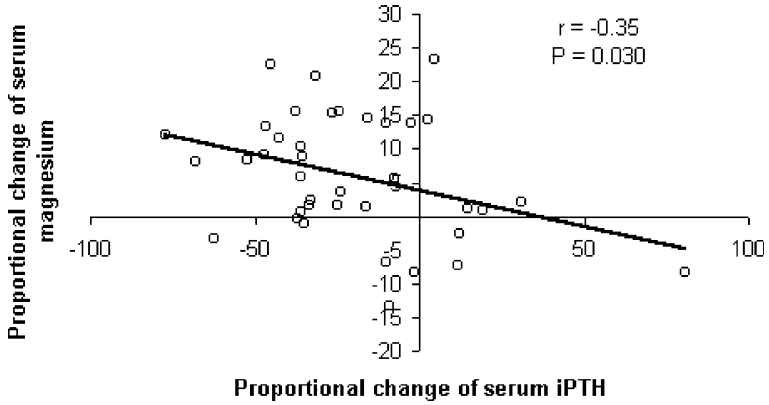

Figure 1. The relationship between the proportional change of serum iPTH and the change of magnesium levels during sevelamer treatment.

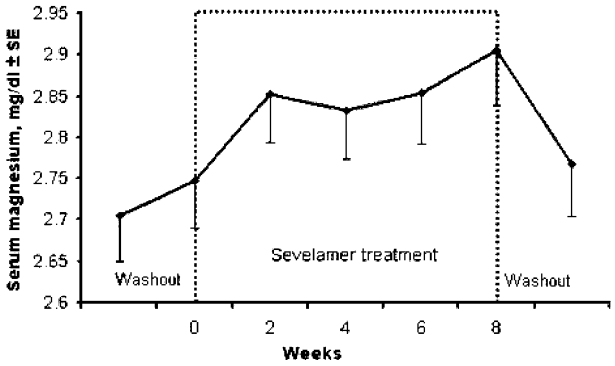

Figure 2. Mean (±SE) serum magnesium concentration during the sevelamer treatment and washout periods.

1.15 ± 0.45 to 1.27 ± 0.48 ($P = 0.009$), which was not only due to the increase in apolipoprotein A1 but also to the reduction in apolipoprotein B. There was no significant association between the changes in lipid profiles and the mean sevelamer dose or the rise in serum magnesium noted during the treatment with sevelamer.

Discussion

Previous studies have documented the ability of sevelamer to reduce serum phosphorus with minimal effects on calcium levels. The current study confirms these findings reporting a significant reduction in serum phosphorus levels during sevelamer treatment, without concurrent changes in serum calcium levels.

The primary objective of our study was to determine the effects of sevelamer treatment on serum magnesium levels; the secondary objectives were to examine possible correlations between changes in serum magnesium and iPTH or lipid profiles.

Sevelamer administration for eight weeks resulted in a significant increase in serum magnesium levels. Mean serum magnesium significantly increased from 2.75 to 2.90 mg/dl ($P < 0.001$) during eight weeks of sevelamer treatment and was significantly reduced after a two week, post treatment washout to 2.77 mg/dl ($P < 0.001$), establishing that the increase in serum magnesium was most probably due to sevelamer administration. The effect of the initially prescribed sevelamer dose (2.4–4.8 g per day) on magnesium was rapid. A substantial increase in serum magnesium levels occurred within two weeks after the initiation of sevelamer. Titration of the drug dose resulted in a further increase in serum magnesium, even though the final mean daily dose of sevelamer (3.5 g) was relatively low. It is noteworthy that in the only study that reported the effect of sevelamer on serum magnesium levels, Chertow et al. [2] noticed a similarly significant rise of 0.1 mg/dl in magnesium concentration, in patients receiving sevelamer for a period of 1 year, at a mean daily dose of 5.3 g.

One might assume that the rise in serum magnesium in our patients could be attributed to the decreased calcium intake, due to the discontinuation of calcium-containing phosphate binders or to nonintentional changes in calcium and magnesium dietary intake, even though patients were asked to avoid any deviations from their usual diet during the study period. Indeed, several experimental studies have suggested that magnesium absorption increases, as dietary calcium decreases, and vice versa [10]. On the other hand, in clinical studies patients with increased rates of calcium absorption, were found to absorb magnesium at a normal rate [11]. In our study, a significant change in serum magnesium was noticed during the treatment period, while during the pre treatment washout period magnesium levels were not significantly altered. In addition, a decline to the pre treatment levels in serum magnesium was seen after the cessation of sevelamer, despite the fact that calcium intake remained constant. Therefore, the rise and decline in serum magnesium levels are directly related to the initiation and cessation of sevelamer even though the possibility of the presence of a diet-related factor cannot be ruled out. Albeit controversial, the presence of sevelamer-induced metabolic acidosis could be another possible explanation for the rise in serum magnesium [12]. Metabolic acidosis has been associated with renal magnesium wasting [13, 14]. On

the other hand, Marone and Sutton [15] found that acute metabolic acidosis had no effect on magnesium excretion. Similarly, acid base disturbances seem to have little or no effect on magnesium redistribution between cells, extracellular fluid and bone [16, 17]. In our study, we have not measured serum bicarbonate concentration and, therefore, a possible contribution of acidosis on measured changes in magnesium levels cannot be ruled out. Another possible mechanism for this effect of sevelamer on magnesium levels could include the binding of bile salts by the drug, resulting in a decrease in the rate of micelle formation in the intestinal lumen. Micelles aggregate free fatty acids, monoacylglycerols, and bile salts, and a decrease in their rate of formation would result in accumulation of free fatty acids in the lumen, which is known to increase intestinal absorption of magnesium [10, 18].

As expected, serum iPTH levels were significantly reduced during sevelamer treatment. Although control of serum phosphorus levels is considered to be one of the most important factors responsible for this decline, the rise in serum magnesium levels may have also contributed. It is known that hypermagnesemia rapidly reduces the secretion of PTH *in vivo*. Cholst et al. [8] have shown that serum PTH concentrations decline rapidly in response to magnesium infusion and stay significantly lower than baseline levels for two hours despite frank hypocalcemia. Moreover, it has been demonstrated that serum magnesium concentrations in dialysis patients are independently associated with PTH levels, suggesting that chronic hypermagnesemia may decrease PTH secretion and/or synthesis [19]. A significant and independent association between the proportional change in serum iPTH and the change in magnesium levels was also noted in our study.

The current investigation demonstrated that sevelamer administration resulted not only in a significant reduction of total cholesterol and LDL cholesterol but also in a significant increase of HDL cholesterol, apolipoprotein A1 and the ratio between apolipoprotein A1 and apolipoprotein B. Triglycerides and apolipoprotein B were unaffected. It has been suggested that the mechanisms responsible for these changes may be similar to those of cholesteramine by binding bile salts. However, the rise in serum magnesium could also contribute to these changes in lipid profiles. It has been shown that magnesium is an effective antihyperlipidemic agent in patients with renal insufficiency [6], in renal transplant recipients [7] as well as in those with type II diabetes [5], hyperlipidemia and ischemic heart disease [4]. In a study by Kirsten et al. [6], 12 weeks of magnesium supplementation in patients with chronic renal insufficiency (serum creatinine greater than 2 mg/dl) resulted in a decrease in serum total cholesterol, from 382 to 282 mg/dl, and in serum LDL cholesterol, from 271 to 176 mg/dl, and in an increase in HDL cholesterol, from 40 to 50 mg/dl. Gupta et al. [7] confirmed that magnesium improves lipid metabolism, as the correction of hypomagnesemia, from 1.81 to 2.18 mg/dl, in nondiabetic renal transplant recipients was associated with reduced serum total cholesterol, from 216 to 192 mg/dl, and LDL cholesterol, from 103 to 96 mg/dl. They conclude that magnesium repletion may be an important ancillary therapy in hypomagnesemic renal transplant patients with hyperlipidemia. In another study by Djurhuus et al., 24 weeks of oral magnesium supplementation in 10 type I diabetic patients increased their serum magnesium levels from 1.80 to 1.92 mg/dl whereas serum LDL cholesterol decreased from 113 to 103 mg/dl [20]. The physiologic and biochemical explanation for this beneficial effect remains still to be fully understood. Several mechanisms have been proposed for the relation between magnesium depletion and the development of hyperlipidemia. Magnesium-deficient rats developed hyperlipidemia as a result of reduction in plasma lipoprotein lipase activity and lecithin cholesterol acyltransferase activity [21]. It has been suggested that the magnesium ion is an important cofactor for both of these enzymes. Jaya and kurup [22] reported that in magnesium-deficient rats there is increased activity of HMG-CoA reductase and increased cholesterol synthesis. It is also believed that a deficiency of magnesium interrupts insulin secretion in the pancreas and increases insulin resistance in the body tissues [23]. Both of these actions may contribute to hyperlipidemia [24].

The significance of the lack of association between the proportional change in serum magnesium concentration and in lipid concentrations is uncertain, as it is known that serum magnesium concentrations do not reflect intracellular magnesium stores. Serum magnesium makes up less than 1% of the total magnesium pool, while bone and

muscle tissues being the main stores. Likewise, it is well known that serum magnesium levels often underestimate the prevalence of magnesium deficiency; it is uncertain whether magnesium administration serves the purpose of merely correcting an underlying deficiency state or of asserting a specific pharmacologic effect of its own [25].

It has also been shown that magnesium is a potent inhibitor of the calcification process and that experimental magnesium deficiency appears to promote arterial calcifications [26]. In addition, observations in end-stage renal disease patients suggested that hypermagnesemia was the only factor that might delay the development of arterial calcifications [9]. Therefore, the rise in serum magnesium by sevelamer could be another contributing mechanism for the favorable effect of sevelamer on arterial calcifications.

The study protocol of Chertow et al. [2] was a long-term trial of one year's duration, during which vitamin D, as well as complementary calcium, could be administered when needed. Both are known to affect magnesium absorption and metabolism. Our study is the first short term trial that confirms a significant rise in magnesium levels after the administration of sevelamer in patients not receiving vitamin D or calcium preparations. In addition, it quantifies the relationship between the changes in magnesium and the changes in iPTH and lipids concentrations.

In conclusion, sevelamer hydrochloride was shown to reduce serum phosphorus, to decrease iPTH and to improve blood lipid profiles in haemodialysis patients. Our findings indicate that, in addition to the above well-established properties, sevelamer treatment results in a significant increase in serum magnesium levels. Increased serum magnesium may contribute to reduction in iPTH levels but this has no effect on changes in lipid levels seen in dialysis patients receiving sevelamer. Longitudinal studies are required in order to determine the long term effects of sevelamer on magnesium levels and to assess the possible clinical implications of increasing serum magnesium in end stage renal disease patients.

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