

DOES SEVELAMER HYDROCHLORIDE (RENAGEL) INFLUENCE 25(OH)D₃ AND 1,25(OH)₂D₃ LEVEL IN HAEMODIALYSIS PATIENTS?

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Introduction

Sevelamer hydrochloride is a non-absorbable resin introduced recently to the therapy of hyperphosphataemia related to chronic renal failure. This non-calcium, non-aluminium containing drug acts by binding phosphate in digestive tract. It was shown in several studies that sevelamer also decreases total cholesterol and LDL-cholesterol concentrations in dialysis patients [1-4]. Recent studies indicate that sevelamer may exert not only antiatherogenic but also anti-inflammatory effect in haemodialysis patients [5]. Sevelamer influences entero-hepatic cycle of bile acids [6] and may lead to decreased absorption of fat-soluble vitamins such as vitamin D. Vitamin D deficiency plays a

crucial role in pathogenesis of secondary hyperparathyroidism and renal osteodystrophy in haemodialysis patients.

The aim of our study was to investigate the influence of therapy with sevelamer on serum concentration of active vitamin D metabolites: 25(OH)D₃ and 1,25(OH)₂D₃ in haemodialysis patients.

1.1 Material and methods

We investigated 10 haemodialysed patients (F=4, M=6), aged 45 ± 12 years (range: 29-67) with mean duration of HD therapy 78 ± 59 months (range: 3 - 158 months). Inclusion criteria were: baseline serum phosphate $> 2,5$ mmol/l and secondary hyperparathyroidism with intact parathormone (PTH) > 400 pg/ml. All of the patients received calcium carbonate to maintain serum calcium at normal level (2,10 - 2,38 mmol/l) at the dose of 2-12 g/d (mean $5,3 \pm 3,2$ g/d). The dose of calcium carbonate did not change during study. Exclusion criteria were: concomitant therapy with active vitamin D, statins or aluminium hydroxide. Also patients with a history of parathyroidectomy and patients with diabetes were also excluded from the study.

Patients were dialysed three times a week, 4-5 hours per session. Bicarbonate dialysate fluid was used with calcium concentration 1,25 mmol/l. The dialysis prescription did not change during study period. The duration of the study was 12 weeks. During the study patients received sevelamer (Renagel, capsules a 403 mg, Genzyme) 3 capsules three times a day, during meals. No dietary changes were advised during the study.

Calcium (Ca) and phosphate (PO₄) concentrations were determined every two weeks during study period, before midweek HD session. At baseline and after 12 weeks of therapy fasting blood was collected for: PTH, 25(OH)D₃, 1,25(OH)₂D₃.

PTH concentration was measured using electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics). For measurement of 25(OH)D₃ and 1,25(OH)₂D₃ concentrations serum samples were stored at -70°C until analysis. Serum 25(OH)D₃ concentration was assessed by competitive ELISA kit (BIOMEDICA Austria). The biologically active 1,25(OH)₂D₃ was extracted with two separate extraction columns. After evaporation, samples were dissolved in ethanol and assessed by competitive ELISA (Immunodiagnostik AG, Germany). The study was performed between November and February in all participants to minimize the seasonal variations in 25(OH)D₃ and 1,25(OH)₂D₃ concentration.

The protocol of the study was accepted by local Ethics Committee. Informed consent was obtained from all patients.

Statistical analysis was performed using Student's t-test, Mann-Whitney test, and linear correlation analysis. Data are expressed as mean \pm SD

1.2 Results

Laboratory findings at baseline and after 12 weeks therapy with sevelamer are presented in Table 1.

In univariate analysis we found only one significant correlation: the changes of PTH correlated with changes of 1,25(OH)2D3 ($r = -0.93$; $p < 0.05$), while no significant correlations were found between PTH and 1,25(OH)2D3 at the beginning of the therapy. Also no significant correlation was found between PTH and 1,25(OH)2D3 at the end of the study. Serum phosphate did not correlate significantly either with PTH or with 1,25(OH)2D3 at the beginning and the end of the study. Sevelamer administration resulted in average 40-50% decrease of vitamin D metabolites at the end of therapy. However this decrease was not statistically significant.

1.3 Discussion

Sevelamer hydrochloride is an effective phosphate binder in haemodialysis patients [2]. Following oral administration sevelamer binds phosphate ions and thus reduces intestinal absorption. Sevelamer also binds bile acids and influences bile acid enterohepatic cycle [6]. This effect may explain the favourable ability of sevelamer to lower total cholesterol and LDL-cholesterol concentration in haemodialysis patients [1-4]. On the other hand this influence may be responsible for drug absorption abnormalities [7]. Recent paper published by Pieper et al. revealed the effect of sevelamer on pharmacokinetics of cyclosporin A and mycophenolate mofetil in transplanted patients [8].

In our preliminary study on the effect of sevelamer on serum concentration of 1,25(OH)2D3 and 25(OH)D3 in haemodialysis patients we found no statistically significant, but borderline decrease of 1,25(OH)2D3 and 25(OH)D3 during therapy with sevelamer. The decrease of 1,25(OH)2D3 and 25(OH)D3 run parallel each other. However both of these values did not correlated in univariate analysis. In the literature we found a limited number of studies regarding the influence of sevelamer on serum vitamin D concentration. Although the results of several studies may indicate that sevelamer influences vitamin D concentration in haemodialysis patients.

In the study by Sadek et al. comparing sevelamer with calcium carbonate in haemodialysis patients, serum 25(OH)D3 concentration decreased in both groups. But in the sevelamer group 6 of 15 patients received alphacalcidol in mean weekly dose of 2,4 ? 1,3 ?g, while nobody received alphacalcidol in calcium carbonate group. Alphacalcidol was given to the patients treated with sevelamer to maintain serum calcium concentration at the same level as in calcium carbonate group. Despite alphacalcidol supplementation in sevelamer group serum 25(OH)D3 concentration did not differ between sevelamer and calcium carbonate group in this study [4].

In the recent study on the effect of sevelamer and calcium on coronary artery calcification in patients new to haemodialysis Block et al. found that proportion of patients using vitamin D increased from 55 to 68% (not significantly) in patients receiving sevelamer, while the proportion of patients on vitamin D remained unchanged (52%) in patients on calcium carbonate. Serum PTH concentration

was higher in sevelamer group [1]. Serum 1,25(OH)2D3 and 25(OH)D3 levels were not evaluated in this study.

Vitamin D deficiency plays a crucial role in the pathogenesis of secondary hyperparathyroidism in dialysis patients. There is no conclusive data regarding the influence of sevelamer therapy on serum 1,25(OH)2D3 and 25(OH)D3 concentration but results mentioned above may indicate potential suppressive effect of sevelamer on intestinal vitamin D absorption. Sevelamer binds bile acids with high capacity [6]. While vitamin D is a fat-soluble vitamin, its intestinal absorption might be impaired in these circumstances. Regarding these data, we believe, that sevelamer presumably depleted 25(OH)D3 by disturbing enterohepatic cycle of vitamin D [7]. As a result of 25(OH)D3 deficiency, its transformation to 1,25(OH)2D3 was diminished. Consequently we did not observe decrease in PTH concentration despite significant decrease in phosphorus concentration. A decrease of serum 25(OH)D3 or 1,25(OH)2D3 levels could be an explanation of the lack of PTH decrease [7]. Also Block et al found that PTH concentration was significantly higher in patients treated with sevelamer than with calcium-based phosphate binders [1].

According to study of others [9], we believe that, depletion of 25(OH)D3 was a primary cause of 1,25(OH)2D3 deficiency. On the other hand, our study showed, that sevelamer therapy restored normal feedback loop from serum 1,25(OH)2D3 on PTH secretion. We suppose that this desired effect was caused by improving of parathyroid gland sensitivity to circulating 1,25(OH)2D3 which had been a result of phosphate decrease [10]. We presume that seasonal variations of 25(OH)D3 may obscure basic effect of sevelamer on serum concentration of 25(OH)D3. Our study was performed during the same season in all patients, hence sevelamer-mediated effect on 25(OH)D3 was noticeable.

Apart from anything, we conclude that sevelamer is a very desirable drug for treating hyperphosphataemia in haemodialysis patients. Our clinical experience confirms this valuable virtue. However it should be noticed that sevelamer may potentially cause interactions with common applied drugs.

1.4 References

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Table 1.

Laboratory findings at baseline and after 12 weeks therapy with sevelamer.

	Baseline	After 12 weeks	P value
Ca(mmol/l)	2.33 ± 0.31	2.35 ± 0.22	0.91
P(mmol/l)	2.94 ± 0.43	2.16 ± 0.48	0.003
Ca x P (mmol ² /l ²)	6.86 ± 1.21	5.06 ± 1.22	0.018
PTH(pg/ml)	1060.2 ± 645.2	1283.1 ± 1079.2	0.23
25(OH)D ₃ (ng/ml)	23.3 ± 11.0	14.3 ± 8.2	0.08
1,25(OH) ₂ D ₃ (pg/ml)	19.5 ± 17.6	10.1 ± 8.5	0.07