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Original article

Short-Term Sole Treatment with Sevelamer Carbonate in Patients on Hemodialysis with High and Low Bone Turnover – Is it Essential for Both Extremes?

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Apstract

Introduction. Chronic kidney disease (CKD) patients on hemodialysis (HD) are burdened with higher co-morbidity and mortality compared to the general population due to the loss of various kidney functions. The maintenance of serum phosphate and calcium homeostasis in end-stage renal disease (ESRD) is severely disrupted. Subsequently, the disordered mineral metabolism stimulates parathyroid glands to secrete higher levels of parathyroid hormone (PTH) in order to maintain normal phosphate and calcium levels. Phosphate binding agents are administered to control hypephosphatemia and to prevent development of hyper parathyroid bone disease (HPTH). Among them non-calcium based one-sevelamer carbonat is preferred for many various benefits.
We aimed to explore the short-term effect of the treatment with sevelamer carbonate in groups of patients with high and low bone turnover assessing the mineral and bone (PTH) parameters.
Methods. We conducted a prospective, postmarketing, two-arm, single center study in maintenance HD patients aged >18 years, with either PTH<150 pg/ml or >600 pg/ml, without previous sevelamer treatment. Based on the PTH level we stratified patients in arm A-PTH <150 pg/ml as presumably adynamic bone disease group (ABD), and arm B-PTH >600 pg/ml, presumed with HPTH. The primary objective was to investigate the efficacy of sevelamer carbonate in HD patients by improving the PTH levels (increase in ABD, and reduction in HPTH patients). The secondary objective was to observe normalization of Ca and P levels and Ca x P product.
Results. The study enrolled in total 23 patients with CKD-MBD, 15 males (65.22%). The average age was 57.03±13.03 years. Older participants developed ABD compared to HPTH (p=0.04). There was no difference found regarding the patients gender (p=0.18). Dialysis vintage showed development of HPTH in patients with longer HD vintage (p=0.04). A significant improvement was observed in the Ca level over the study course, while the phosphate (P) level worsened from 1.96 to 2.15 (p=0.03) in the first month and returned to 1.96 (p=0.95) at the study end (3 months). The Ca x P product level did not change during the study in the whole cohort. The PTH significantly increased (p=0.00) but remained in the reference range for HD patients.
There was a significantly lower level of calcium at the end of the study (p=0.01) in the ABD group, the phosphate levels tend to further increase, while PTH levels significantly improved towards the reference range.
In the HPTH group, there was an improvement in the calcium level compared to baseline and trend for an increase in the phosphate levels that leveled off at the end of the study. In contrast, the level of alkaline phosphatase and PTH significantly increased over time.
Conclusion. The study met the primary objective by increasing the PTH level in ABD patients. Additionally, normalization of Ca and P levels and Ca x P product was achieved only for the Ca level in the ABD arm. Relatively small sample size and short time period might have been the reasons for not reaching all secondary objectives.
The level of PTH and alkaline phosphatase could not have been controlled over the course of the study in patients with HPTH. Hence, a higher dose of sevelamer carbonate in combination with vitamin D is required in order to adequately suppress PTH levels in patients with already established HPTH.

Key words: sevelamer carbonate, phosphate, calcium, parathyroid hormone

Introduction

Chronic kidney disease (CKD) patients on maintenance hemodialysis (HD) treatment are burdened with higher comorbidity and mortality compared to the general

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population due to the loss of various kidney functions with the maintenance of serum phosphate and calcium homeostasis as crucial one. Along with the CKD progression to end-stage renal disease (ESRD) the excretion of phosphate is impaired, and there is a reduction in the synthesis of 1 α-hydroxylase and vitamin D leading towards hyperphosphatemia and hypocalcemia. Thus, if appropriate measures are not taken, the parathyroid glands begin secreting higher levels of parathyroid hormone (PTH) in order to maintain normal levels of phosphate and calcium by stimulating the synthesis of 1 α-hydroxylase and inhibiting phosphate resorption. Ultimately, these compensatory mechanisms are overcome due to renal function loss and ensuing secondary hyperparathyroidism [1].

The result from these metabolic disturbances are all named chronic kidney disease-mineral and bone disorders (CKD-MBD) [2,3]. Clinically it comprises of several bone conditions known as renal osteodystrophy (ROD) that range from high bone turn-over i.e. hyperparthyroid bone disease (HPTH) to low bone turn-over state or adynamic bone disease (ABD). In between are conditions named as osteomalacia and mixed lesions, possibly combined with osteoporosis [4,5].

All ROD patterns share almost similar symptoms with bone and joint pain, muscle weakness, increased fracture rate, and also extra osseous bone depositions of phosphate and calcium in soft tissues and in the vascular bed [6]. Such vessels are stiffer and fail to react to change in the blood flow because of the lower elasticity. There are increasing epidemiological findings that there is a positive correlation in cardio-vascular and all-cause morbidity and mortality in these patients associated with vascular calcification [7,8].

Primary focus in the management of CKD-MBD is to treat hyperphosphatemia. Main sites responsible for maintenance of normal level of phosphate are the gastrointestinal tract and kidneys. The main source of phosphate in ESRD patients is through the dietary intake of protein rich food. Dietary restriction is seldom a choice of phosphate lowering treatment option due to the risk of protein malnutrition. Standard 4-hours high flux HD treatment removes around 800 mg of phosphate per treatment and is not sufficient enough to remove all of the daily phosphate intake and thus CKD-MBD cannot be effectively controlled.

Considering the fact that the kidneys in ESRD are incapable to regulate the phosphate excretion, an option to control the phosphate level is to reduce the amount of phosphate resorption in the small intestines by phosphate binders. Several phosphate binders can be used in patients who are on chronic HD regimen: aluminium and calcium-based salts, and non-aluminum, non-calcium-based phosphate binders like sevelamer hydrochloride and from recently sevelamer carbonate with an improved safety profile [9]. Calcium-based salts could achieve a good control of phosphate level but this is usually followed with hypercalcemia as adverse effect, in around one-third of patients with ESRD. In addition, the hypercalcemia *per se* is associated with an increased risk of vascular calcification [10].

Thus, the most widespread non-calcium-based phosphate binder alternative today is sevelamer hydrochloride, and even better with carbonate composite. Structurally it is a cationic hydrogel, a polimer containing polyallylamine chloride cross-linked with epichlorohydrin, which makes it being hydrophilic but insoluble in water. It is not absorbed from the gastro-intestinal tract and binds phosphate in exchange for chloride ideally at pH 7 [11,12]. In addition, there are a couple of pleiotropic effects concerning the lipid lowering ability and amelioration of acidosis in CKD patients [13].

Material and methods

We conducted a prospective, postmarketing, comparative, two-arm study from 12th December 2018 till 13th March 2019 in a single dialysis center. Inclusion criteria were: ESRD patients older than 18 years undergoing hemodialysis trice weekly, with abnormal level of PTH (below 150 pg/ml and above 600 pg/ml) and have not used sevelamer as phosphate binder in the previous six months.

Study participants were stratified into two arms regarding the level of PTH; Arm A enrolled participants with PTH level < 150 pg/ml (ABD group), and Arm B participants with PTH level >600 pg/ml (HPTH group). The dosing of sevelamer carbonate was dose dependent based on the phosphate blood level (P=1.7-2.1-3 x 0.8 g/daily; P=>2.1-2.6-4 x 0.8 g/daily; P>2.6-5 x 0.8 g/daily). There were no study participants who were discontinued from the study for any reason. Local Ethics Committee approved the study protocol and each study participant signed an Informed Consent prior their enrollment into the study.

The primary objective of the study was to investigate the efficacy of sevelamer carbonate in improving the PTH levels (an increase in ABD patients, and reduction in patients with HPTH). The secondary objective was to observe normalization of the level of Ca, P and calcium x phosphate product.

Demographic characteristics of participants were noted at the study entry. Clinical and laboratory variables were recorded at baseline and with subsequent measurements in the following three months.

The variables that were collected and analyzed were serum levels of calcium, phosphate, PTH, alkaline phosphatase, C-reactive protein, hemoglobin, ferritin. Clinical parameters that were examined were blood pressure and mean arterial pressure from three separate measurements during HD prior to study entry, and in the following three months. Each of the study laboratory variables estimated as an average value of the previous six months was also noted as an average before the study entry baseline value, and monthly values were

recorded in the following three months. The average number of calcium carbonate tablets and average dosage of calcitriol were also noted in the same period. The descriptive statistics of the patients is shown as frequency (percentage). The continuous variables were shown as mean and standard deviation (SD). Intra-patient comparison of clinical and laboratory variables was computed using T-test for normally distributed samples. Relationship between qualitative variables was evaluated by chi-square test. P values less than 0.05 was considered statistically significant. All statistical analysis were performed using IBM Statistical Package for the Social Sciences® (SPSS) software platform, issue 15.0 Command Syntax Reference. Chicago, Illinois: SPSS Inc. 2006.

Results

This study enrolled in total 23 patients with CKD-MBD, 15 males (65.22%). The average age of the study population was 57.03±13.03 years, for patients with HPTH 51.78±16.63, and for those with ABD 61.07±8.98 years that were predominantly older age males (78.6%). Demographic characteristics of the participants at study entry are shown in Table 1.

Patients' age was shown to be associated with various CKD-MBD state, whereas older study participants developed ABD compared (p=0.04). No significant difference was found regarding the gender (p=0.18). Comparison between primary cause of ESRD showed no impact of DM type II presence on bone metabolism (p=0.18). Dialysis vintage showed development of

Table 1. Demographic characteristics of participants at study entry

	Study population N = 23	**Arm A Adynamic bone disease** N=14	**Arm B Hyperparathyroidism** N=9	**P value**
Gender				0.18
Female	8(34.78%)	3(21.43%)	5(55.56%)	
Male	15(65.22%)	11(78.57%)	4(44.44%)	
Age	57.43±13.03	61.07±8.98	51.78±16.63	**0.04***
Female	55±19.99	68±7.55	47.2±21.63	0.08
Male	58.73±7.86	59.18±8.67	57.5±5.92	0.36
Primary cause of ESRD				0.18
GN	6(26.09%)	3(13.04%)	3(13.04%)	
DM II	6(26.09%)	1(4.35%)	5(21.74%)	
HTA	5(21.73%)	4(17.39%)	1(4.35%)	
ADPKD	2(8.7%)	1(4.35%)	1(4.35%)	
Others	4(17.39%)	1(4.35%)	3(13.04%)	
HD vintage (y)	7.13±5.22	5.57±5.4	9.56±4.07	**0.04***

Abbreviations: Data expressed as mean ±SD-Standard deviation; ESRD-End Stage Renal Disease; HD-Hemodialysis; GN=glomerulonephritis; DM diabetes mellitus; HTA- hypertension; ADPKD-adult dominant polycystic kidney disease; Others-nephrocalcinosis, Wegener granulomatosis, systemic lupus erythematosus. *P value significant between the groups

Table 2. Laboratory variables in all study participants

	Average	**Baseline***	**1st measurement**	**2nd measurement**	**3rd measurement**
Ca	2.28±0.2	2.39±0.23	2.22±0.19 (**p=0.00**)	2.21±0.18 (**p=0.00**)	2.25±0.20 (**p=0.00**)
P	1.98±0.23	1.96±0.33	2.16±0.39 (**p=0.04**)	2.15±0.37 (**p=0.03**)	1.96±0.36 (p=0.95)
Ca x P	4.54±0.73	4.67±0.95	4.79±0.86 (p=0.53)	4.73±0.88 (p=0.67)	4.43±1.03 (p=0.36)
AF	198.87±363.00	188.78±351.90	175.84±288.34 (p=0.38)	197.78±374.29 (p=0.25)	222.00±374.12 (**p=0.00**)
PTH	412.77±553.29	421.39±542.74	486.13±529.70 (p=0.1)	422.27±394.44 (**p=0.02**)	*600.25±599.79 (**p=0.00**)
CRP	9.26±10.09	12.69±25.93	15.49±25.48 (p=0.65)	9.23±20.87 (p=0.47)	11.00±19.04 (p=0.75)
Hb	115.13±6.69	113.65±10.29	116.00±9.18 (p=0.15)	115.03±10.06 (p=0.47)	117.22±9.97 (p=0.75)
Ferritin	170.18±117.22	196.22±142.27	210.83±129.46 (p=0.52)	183.47±100.62 (p=0.61)	322.51±238.47 (**p=0.01**)

Abbreviations: Ca, calcium (mmol/L); P, phosphate (mmol/L); Ca x P, calcium x phosphate product; AF, alkaline phosphatase (U/L); PTH, intact parathyroid hormone; CRP, C Reactive Protein; Hb, hemoglobin (g/L). *P value statistics versus baseline values

HPTH in patients with longer HD vintage (p=0.04).
From the clinical variables, the mean arterial pressure of the whole cohort did not change over time. The average value prior the study entry was 102.35 mmHg±12.94, followed by 101.3 mmHg ±12.02 in the first month, and 104.65 mmHg ±9.18 (p=0.48) and 103.91 mmHg ±12.32 (p=0.34) in the second and third month, respectively. In addition, there was no significant change in the body weight (BW) after dialysis treatment over the course of the study period.
Comparison of the laboratory variables of the whole study population is shown in table 2. A significant change was observed in the level of calcium over the study period, the level of phosphate was worsened from 1.96 to 2.15 (p=0.03) in first month and returning to 1.96 (p=0.95) at the end of the study. The level of calcium x phosphate product did not change during the study in the whole cohort. The PTH significantly increased (p =0.00) but remained in the reference range for patients on HD. There was also change in the markers of inflammation (ferritin increase, p= 0.01).
The average dose of calcium-containing phosphate binders in all of the participants prior to entry of the study was 3.97g±1.17 and of calcitriol was 0.8 mcg±1.71. The dosage of sevelamer carbonate was titrated in relation to the level of phosphate, average values were 2.68 g± 0.57, 2.68 g±0.57 and 2.61 g±0.5 at the subsequent measurements (Table 3). Slightly higher doses of sevelamer were prescribed in HPTH patients but it didn't reach statistical difference.

Table 3. Sevelamer dosage and significance in all study participants and between groups

	Baseline*	1st measurement	2nd measurement	3rd measurement
Sevelamer (all study participants)	2.68±0.46	2.68±0.57 (p=1.00)	2.68±0.57 (p=1.00)	2.61±0.50 (p=0.16)
Sevelamer (arm ABD)	2.63±0.49	2.57±0.56 (p=0.34)	2.57±0.56 (p=0.34)	2.57±0.56 (p=0.34)
Sevelamer (arm HPTH)	2.76±0.42	2.84±0.58 (p=0.68)	2.84±0.58 (p=0.68)	2.67±0.40 (p=0.35)

Abbreviations: ABD-Adynamic Bone Disease; HPTH-Hyperparathyroid bone disease; *P value statistics versus baseline values

In addition, the analysis was performed for each of the groups in the study, separately. Given the differences in the development, symptoms, treatment and outcome in the ABD and HPTH the results was expectedly different.
Vitamin D was not administered at the beginning of the study in order to omit any confounding effect on the sevelamer treatment, but after the second measurement in a single patient of ABD group (significantly increased PTH) and in the majority of patients in HPTH group (0.11±0.40 vs 4.06 ± 2.58, p<0.001, respectively).
The results from the study Arm ABD are shown in Table 4. There was a significantly lower level of calcium at the end of the study (p=0.01), the phosphate levels tend to further increase, while PTH levels significantly improved towards the reference range. There was no change in the level of markers of inflammation.
The results from the study Arm HPTH are shown in Table 5.
In the HPTH group, it can be observed that there is an improvement in the calcium level compared to baseline

Table 4. Laboratory variables in Arm ABD

	Average	Baseline*	1st measurement	2nd measurement	3rd measurement
Ca	2.23±0.17	2.35±0.22	2.12±0.10 **(p=0.01)**	2.12±0.09 **(p=0.01)**	2.17±0.16 **(p=0.01)**
P	1.99±0.27	1.89±0.37	2.17±0.47 (p=0.08)	2.17±0.45 **(p=0.03)**	2.01±0.36 (p=0.32)
Ca x P	4.46±0.81	4.44±1.01	4.59±0.93 (p=0.62)	4.61±0.97 (p=0.5)	4.38±0.94 (p=0.86)
AF	77.06±19.29	80.93±36.86	77.46±18.99 (p=0.61)	197.78±374.29 (p=0.92)	222.00±374.12 (p=0.15)
PTH	86.25±50.54	88.93±63.64	77.46±72.98 **(p=0.01)**	150.93±93.15 **(p=0.00)**	198.32±119.88 **(p=0.00)**
CRP	11.40±11.87	19.06±32.02	14.25±23.50 (p=0.52)	12.94±26.33 (p=0.44)	15.45±23.41 (p=0.68)
Hb	113.09±6.94	109.21±10.58	113.29±10.10 (p=0.07)	112.93±12.06 (p=0.21)	115.36±10.56 (p=0.12)
Feritin	162.07±128.46	187.79±154.13	182.36±114.81 (p=0.87)	155.99±88.32 (p=0.39)	278.02±244.24 (p=0.15)

Abbreviations: Ca, calcium (mmol/L); P, phosphate (mmol/L); Ca x P, calcium x phosphate product; AF, alkaline phosphatase (U/L); PTH, intact parathyroid hormone; CRP, C Reactive Protein; Hb, hemoglobin (g/L). *P value significance versus baseline values

Table 5. Laboratory variables in Arm HPTH

	Average	Baseline*	1st measurement	2nd measurement	3rd measurement
Ca	2.36±0.22	2.45±0.23	2.38±0.19 **(p<0.05)**	2.34±0.20 **(p<0.05)**	2.37±0.19 **(p<0.05)**
P	1.98±0.16	2.06±0.23	2.15±0.24 (p=0.29)	2.10±0.23 (p=0.47)	1.89±0.35 (p=0.26)
Ca x P	4.67±0.60	5.02±0.77	5.11±0.65 (p=0.70)	4.93±0.74 (p=0.58)	4.52±1.22 (p=0.25)
AF	365.35±552.13	356.56±535.09	328.89±429.84 (p=0.47)	380.78±568.11 (p=0.14)	418.89±558.64 **(p=0.00)**
PTH	984.18±572.06	938.56±556.03	1032.00±460.68 (p=0.36)	898.25±209.17 (p=0.19)	1303.64±404.99 **(p=0.01)**
CRP	5.95±5.55	2.78±1.03	14.25±23.50 (p=0.52)	12.94±26.33 (p=0.44)	15.45±23.41 (p=0.68)
Hb	118.29±5.15	120.56±4.61	113.29±10.10 (p=0.07)	112.93±12.06 (p=0.21)	115.36±10.56 (p=0.12)
Feritin	182.80±103.31	2097.33±129.38	182.36±114.81 (p=0.87)	155.99±88.32 (p=0.39)	278.02±244.24 (p=0.15)

Abbreviations: Ca, calcium (mmol/L); P, phosphate (mmol/L); Ca x P, calcium x phosphate product; AF, alkaline phosphatase (U/L); PTH, intact parathyroid hormone; CRP, C Reactive Protein; Hb, hemoglobin (g/L). * P value significance versus baseline values

and trend for an increase in the phosphate levels that leveled off at the end of the study. Almost the same pattern was observed for the CaxP product. In contrast, the level of alkaline phosphatase and PTH significantly increased over time. Again in this study arm, there was no change in the level of markers of inflammation.

Discussion

Bone and mineral abnormalities have a major impact on morbidity and mortality in patients with CKD treated with dialysis. Additionally, hyperphosphatemia as an integral component of the CKD-MBD syndrome has been associated with increased mortality and with the development of cardiovascular calcification, an independent predictor on mortality [14]. Several treatment strategies were investigated in clinical trials and routine practice for management of CKD-MBD in dialysis patients. Almost all of them used calcium-containing phosphate binders with consecutive risks of soft tissue calcifications. Discovery of sevelamer, as non-calcium based phosphate-binding agent, brought some light in reducing those treatment related complications, reducing the morbidity and mortality rates. The effect of sevelamer had been investigated in several clinical studies. Reasonably, it has been shown that it causes smaller increase in calcium levels compared to calcium-containing phosphate binders [15,16]. The Treat-to-Goal study, randomized study which enrolled 200 hemodialysis patients to take either sevelamer or calcium-based phosphate binders demonstrated a decrease in phosphate of approximately 2.5 mg/dL and Ca×P of approximately 20 mg/dL in both groups (P=0.33 and P=0.12, respectively), but with an 0.4 mg/dL increase in serum calcium in the calcium-treated group, compared to 0.1 mg/dL in the sevelamer group (P=0.002) [17]. Another study showed serum levels of phosphate, calcium, and intact parathyroid hormone were well controlled within both study groups, calcium-containing phosphate binders and sevelamer group with consistently lower calcium and higher iPTH [18].

In our study significantly decreased levels of calcium in ABD patients (p=0.01), may reduce the risk of soft tissue calcification, indirectly lowering the impact on the level of PTH and thus possibly improving the effect on bone metabolism. This also may go in line with the well reduced risk of calcification in patients receiving sevelamer. Regarding the level of calcium x phosphate product, unlike the other studies, it did not change significantly (p=0.77). The phosphate level in ABD group started to increase significantly over the course of the study, although did not reach statistical significance at the study end (p=0.26). However, the upper normal level of phosphate directly stimulates the secretion of PTH and the bone metabolism slowly returns to its' normal state of daily bone mineral turnover, possibly continuing with the beneficial impact stated previously. In this regard, the level of PTH increased significantly (p=0.01), followed by the increasing trend of alkaline phosphatase (p=0.15) compared to baseline value, and one may speculate this state may be viewed as a sign of a gradual bone recovery.

Several studies had shown the beneficial effect of the sevelamer use in lowering blood phosphate levels. In the prospective randomized Renagel in New Dialysis Patients (RIND) trial, there was relatively less progression of coronary artery calcification in 127 incident hemodialysis patients randomly assigned to sevelamer versus calcium-based phosphate binders [19]. An another two-year study has supported the findings that calcium carbonate use is continuously associated with progressive arterial calcification in haemodialysis patients [20]. In addition, while it may be associated with a decreased trabecular bone density, the beneficial effect of sevelamer on bone has been shown in several other studies [21,22]. Anibal *et al*. found that phosphate control with

sevelamer resulted in no statistically significant changes in bone turnover or bone mineralization compared with calcium-based binders, but bone formation was significantly increased with sevelamer, being also associated with improved trabecular architecture.[13]

In the HPTH arm of our study, the phosphate control remained stable over the study course, with significantly reduced calcium levels compared to baseline (p=0.02). Expectedly, almost the same pattern was observed for the CaxP product while, the level of PTH and alkaline phosphatase significantly increased over time. It could be partially explained by both known PTH stimulus, i.e. lower calcium and a higher phosphate levels, and somewhat late vitamin D administration in the third month of the study. Importantly, even higher vitamin D doses could have been administered in order to adequately suppress PTH in the absence of potential high calcium absorption from calcium based binders. Hence, higher doses of vitamin D could be safely used knowing that sevelamer limits the risk of hypercalcemia, in order to control PTH and HPTH.

In both study arms there was no change in the level of markers of inflammation, something that was observed as pleiotropic effect in other studies.[23,24] The effect by which sevelamer reduces inflammation is not quite understood, there is one study that states that it binds endotoxins in the intestinal lumen, but no clinical trials have been performed to investigate this hypothesis [25]. In addition, improving the acidosis may slow the rate of kidney function decline and potentially reduce the risk of ESRD in patients with CKD and metabolic acidosis [26].

Finally, about some study limitations. It's surely the relatively small sample size, but all patients were enrolled from a single center that met the inclusion criteria. Second, the time period of the study was relatively short that might have been one of the reasons for partial achievement of the study objectives.

Conclusion

The short-term treatment with sevelamer increased PTH in ABD patients, which in turn may possibly improve the bone turnover and symptoms of CKD-MBD. There was also normalization of the level of Ca and slight increase in phosphate towards upper level of normal that in turn was in fact a potent stimulus for PTH increase.

The level of PTH and alkaline phosphatase could not have been controlled over the course of the study in patients with HPTH, along with no significant change in the levels of Ca and P. Hence, a higher dose of sevelamer carbonate in combination with vitamin D should be administered in order to adequately suppress PTH levels in patients with already established HPTH.

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