Efficacy and safety of sevelamer

Comparison with calcium carbonate in the treatment of hyperphosphatemia in hemodialysis patients

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ABSTRACT

Objective: Current phosphate binders used in hemodialysis patients include calcium-based binders that result in frequent hypercalcemia. The use of a calcium- and aluminum-free phosphate-binding polymer in hemodialysis (sevelamer) disclosed efficacy in the short and long-term studies. However, due to race differences we performed a short-term study on the Saudi hemodialysis patients and compared sevelamer with a standard calcium-based phosphate binder.

Methods: An open-label, randomized, cross-over study was performed to evaluate the safety and effectiveness of sevelamer hydrochloride in controlling hyperphosphatemia in hemodialysis patients. After a 2-week phosphate binder washout period, stable hemodialysis patients were given either sevelamer or calcium carbonate, and the dosages were titrated to achieve phosphate control over an 8-week period. After a 2-week washout period, patients crossed over to the alternate agent for 8 weeks. Twenty patients from the Dialysis Unit of King Fahd Hospital, Jeddah, Kingdom of Saudi Arabia, were recruited for the study between March 2003 and June 2003.

Results: There was a similar decrease in serum phosphate values over the course of the study with both sevelamer (-3.3 ± 2.2 mg/dL) and calcium carbonate (-3.9 ± 2.8 mg/dL). Fifty-two percent of patients developed serum calcium greater than 2.75 mmol/L (11.0 mg/dL) while receiving calcium carbonate versus 26% of patients receiving sevelamer ($p<0.05$). The incidence of hypercalcemia for sevelamer was not different from the incidence of hypercalcemia during the washout period. Patients treated with sevelamer also sustained a 13% mean decrease in serum cholesterol levels.

Conclusion: Sevelamer was effective in controlling hyperphosphatemia without resulting in an increase in the incidence of hypercalcemia seen with calcium carbonate. This agent appears quite effective in the treatment of hyperphosphatemia in hemodialysis patients, and its usage may be advantageous in the treatment of dialysis patients.

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Several short-term clinical studies in patients with end-stage renal disease have established that sevelamer is as efficacious as calcium carbonate or acetate at lowering serum phosphorus, and is well tolerated.[1-3] Furthermore, short-term control of hyperparathyroidism has proved to be adequate, with maintenance of normal serum calcium concentrations, and significant decreases in the phosphate x calcium product. In addition, short-term favorable effects on the lipid profile have

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been observed with 20-30% decrease in low density lipoprotein (LDL) cholesterol, and a 5-15% increase in the high density lipoprotein (HDL) cholesterol concentrations, presumably related to the binding of the bile acids to the compound. There is a study of the long-term safety and effectiveness of sevelamer at controlling hyperphosphatemia.[4] Race is a major factor in determining the clinical course of diverse kidney disorders[5] and responses to medications.[6] Accordingly, variation may exist in different patient populations.

The aim of this study is to determine the efficacy and safety of sevelamer hydrochloride as a hypophosphatemic agent in the Saudi chronic hemodialysis patients in the Kingdom of Saudi Arabia (KSA), and to compare it to the calcium carbonate used currently for this purpose in this population.

Methods. This is an open-label cross-over prospective study of Sevelamer (Renagel, manufactured by Genzyme Corporation, Cambridge, MA, USA) on adult chronic hemodialysis patients with hyperphosphatemia performed between March 2003 and June 2003. There were 20 study patients from King Fahd Hospital, Jeddah, KSA, who received sevelamer and calcium carbonate according to the inclusion criteria with washout periods for the crossover. The patients served as their own controls. The patients recruited were of age between 15 and 75 years inclusive, maintained on chronic hemodialysis (2 or 3 times weekly) for at least 3 months and optimally dialyzed as judged by usual dialysis and serum chemistry parameters. The current phosphorus blood level should be more than 1.8 mmol/L (5.5 mg/dl). The patients had no serious gastrointestinal disease including dysphasia, vomiting, motility disorder, major intestinal surgery, or markedly irregular bowel function. The patients did not abuse alcohol or drug dependence. The patients did not have clinically relevant liver disease, uncontrolled diabetes or uncontrolled hypertension, malignancy, human immunodeficiency virus infection, active vasculitis or illness at the time of entry to the study. The investigator had informed the patients of all the risks and benefits of the study and the patients signed the informed consent before the start of the study. Routine concomitant medications were allowed.

At the entry of patients to the study, each patient had history and physical examination including detailed history of renal disease and bone disease, in addition to the current therapies. There was an estimate of diet phosphate daily intake. Baseline laboratory investigations included complete blood count, hepatitis screen (C and B types), electrolytes, calcium, phosphate, liver function tests, blood glucose, urea, creatinine, cholesterol, triglycerides and whole molecule intact parathyroid hormone. The duration of the study included 2 stages with 2 weeks of washout period in between. At the entry to the study, phosphate binders were discontinued. After 2 weeks washout period, the patients were randomly allocated to receive either sevelamer or calcium carbonate for 8-weeks. After a second washout period of 2-weeks, the patients were crossed-over to the alternate agent for 8-weeks. The starting dose of sevelamer was 800 mg tablets orally 3 times per day post meals. The starting dose of calcium carbonate (caltrate 600) was one 1500 mg tablet post meals 3 times a day (600 mg of elemental calcium equates 1500 mg calcium carbonate, since calcium carbonate is 40% calcium). The dose of either medication was adjusted in order to reach control of phosphorus (level of 0.8-1.8 mmol/L or 2.5-5.5mg/L). In case it was necessary, there was an increment or decrement of doses every 2-weeks by adding one tablet 3 times a day to keep the levels of phosphorus within normal limits.

All the patients were dialyzed on 1.75 mmol/l (3.5mEq/l) dialysate calcium concentration and had no change of their prescribed phosphorus intake (one gram daily) during the study period. Vitamin D dosage was not changed during the study period. Compliance to hypophosphatemic therapy was determined by pill count of the sevelamer and calcium carbonate. Percent compliance was determined by the total number of tablets taken divided by the total number prescribed. We followed-up the efficacy of the hypophosphatemic therapy by weekly monitoring of the serum phosphate, calcium and albumin. Complete blood count, liver function tests, alkaline phosphatase, urea and creatinine, electrolytes, cholesterol, triglycerides and parathyroid hormone were performed in week 2, 6, 10, 12, 16 and 20 from the start of the study. The blood samples were drawn at the beginning of the second dialysis session of the week for all patients. The physical examination was repeated at the end of the study period. If the patient was offered a renal transplant during the course of the study, they would be withdrawn from the treatment with sevelamer. However, in case of irreversible renal rejection and transplant nephrectomy the patient could reenter the study. We closely monitored the safety and tolerability of the therapy including the time of onset of any reaction in relation to the administration of sevelamer. Furthermore, the severity of the reaction, its duration and any action taken, as well as the outcome was recorded in the case report form. The relationship of any adverse reaction to the administration of sevelamer was assessed following thorough consideration of all the facts available.

Statistical methods. All data were compiled descriptively in tables and graphs. The main parameters of efficacy were the doses necessary to

reach and maintain the target range of phosphorus. The safety was assessed by the laboratory parameters, the vital signs and the incidence of adverse reactions. The sample was stratified by various baseline variables (phosphorus and calcium levels, age, weight, time on dialysis and investigator) in order to generate possible hypotheses of influence of those variables on response. Serum calcium was adjusted for serum albumin according to described formula.[7] We used the analysis of variance to compare the equality of means for any of the 3 or more groups of quantitative variables such as age, phosphorus level, and so forth. The 2 samples independent t-test were used to compare the equality of the means for any of the 2 groups. Chi-square test was used to compare categorical variables such as gender, weight, and so forth. The *p* value was set as significant if below 0.05.

Results. Seventeen patients completed both treatment sequences. The other 3 completed one sequence; 2 sevelamer and one calcium. The first patient completed 8-weeks therapy of calcium carbonate and discontinued the study during the sevelamer phase due to renal transplantation. The second patient completed sevelamer phase but died on the third week of the calcium carbonate phase due to cardiac event. The third patient completed the sevelamer phase and moved to another center during the third week of the calcium carbonate phase. There were 19 cases in the sevelamer group to compare with 18 in the calcium carbonate group. **Table 1** shows the baseline characteristics of the patients. The baseline serum calcium level was 9.4 ± 1.2 mg/dL. All patients received oral calcitriol with a mean dose of 2.1 ± 1.08 mg/week. The mean starting dosage of calcium carbonate was 4.5 g/d (1.8 g/d of elemental calcium), which increased to 9 g/d (3.2 g/d of elemental calcium) by the end of 8-weeks of treatment. For sevelamer, the mean starting dosage was 2.4 g/d and increased to 5.2 g/d at the end of 8-weeks. Patients were 88% compliant with sevelamer and 96% with calcium carbonate by pill count. The occurrence of adverse events was similar for each treatment. Gastrointestinal complaints occurred during sevelamer treatment in 28% of patients versus 35% during calcium carbonate treatment. The incidence of nausea, vomiting, diarrhea, and constipation was not statistically different between groups. No serious adverse events related to medication occurred during the treatment.

Statistical analysis showed no sequence effect for the efficacy parameters studied, the results of the 2 sequences were combined. **Table 2** shows the change in serum phosphorus for the 2 sequences combined. Although the mean baseline serum phosphorus concentration was not significantly different before treatment with sevelamer and calcium carbonate (8.6 ± 2.4 mg/dL versus 8.4 ± 1.9 mg/dL, the mean change in serum phosphorus from

Table 1 - Patients characteristics.

Characteristics	n
N	20
Age (year)	42.7± 9.9*
Gender (%)	
Male	60
Cause of end-stage renal disease (%)	
Diabetes mellitus	20
Hypertension	10
Other	70
Duration of dialysis (year)	3.4 ± 1.6*
History of parathyroidectomy (%)	5
Usage of vitamin D analogue (%)	100
Oral (%)	100
Intravenous (%)	none
Serum albumin (g/dL)	4 ± 0.3*
Dialysis dosage (Kt/V)	1.2 ± 0.4*

*mean ± standard deviation

Table 2 - Laboratory parameters by treatment sequence.

Parameters	Sevelamer *	Calcium carbonate*	*p* value
Serum phosphorus (mg/dl)			
Baseline	8.0 ± 1.8	8.2 ± 2.1	0.74
Final	5.7 ± 1.2**	4.9 ± 0.7***	
Change	-2.9 ± 1.9	-2.7 ± 1.4	
Adjusted serum calcium (mg/dL)			
Baseline	9.4 ± 1.2	9.6 ± 1.1	0.1
Final	9.3 ± .8	10.0 ± 1.4	
Change	-0.2 ± 0.9	0.5 ± 1.3	
Serum calcium x phosphorus product (mg² /dL²)			
Baseline	82.5 ± 26.3	82.5 ± 25.4	0.4
Final	50.8 ± 16.0	45.0 ± 14.6	
Change	-31.7 ± 24.2	-37.5 ± 34.7	
Serum iPTH (pg/ml)			
Baseline	159 ± 134	135 ± 133	0.8
Final	97 ± 114	91 ± 87	
Change	-45 ± 143	-53 ± 152	

Intact iPTH normal values: 15-65 pg/ml, *mean ± standard deviation, ** $p<0.003$ in comparison with baseline, *** $p<0.005$ in comparison with baseline, iPTH - intact parathyroid hormone

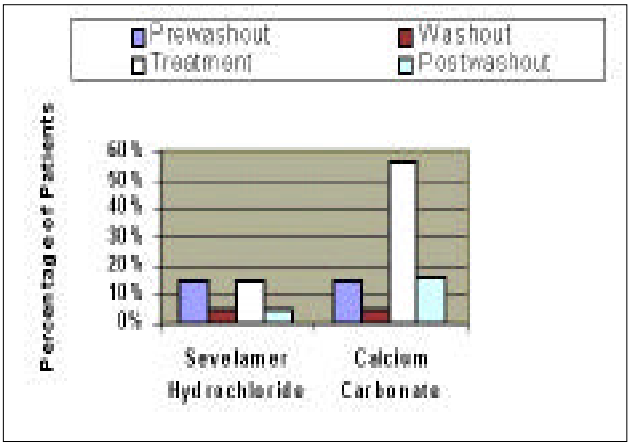

Figure 1 - Percentage of patients who developed at least one episode of hypercalcemia (adjusted serum calcium >11 mg/dL) during the prewashout, washout, treatment, and postwashout periods, $p<0.05$.

Table 3 - Effect of sevelamer hydrochloride and calcium carbonate on serum lipid values.

Variable	Sevelamer hydrochloride*	Calcium carbonate*	*p value*
Total cholesterol (mg/dL)			
Baseline	149 ± 29	148.6 ± 33	
Final	131 ± 34	143 ± 23	
Change	-18 ±13	-5 ± 25	0.16
Triglycerides			
Baseline	158 ± 50	139 ± 55	
Final	140 ± 49	141 ± 36	
Change	-21 ± 36	7 ± 57	0.15

Normal ranges = total cholesterol was <200 mg/dL) and triglycerides was <200mg/dL. *Mean ± Standard deviation

baseline to the end of treatment was similar between treatments (-3.3 ± 2.2 mg/dL with sevelamer and -3.9 ± 2.8 mg/dL with calcium carbonate). There was a 0.2 mg/dL decrease of the adjusted serum calcium during sevelamer treatment, while there was a 0.5 mg/dL increase of it during the treatment with calcium carbonate (**Table 2)**. An episode of hypercalcemia, defined as a serum calcium greater than or equal to 11.0 mg/dL, occurred in 15% of patients during 8-weeks of sevelamer treatment and 56% of patients during 8-weeks of calcium carbonate treatment ($p<0.05$), (**Figure 1)**. Furthermore, there were a total of 13 episodes in the sevelamer group versus 33 episodes in the calcium carbonate group during the treatment period; the check points were at the end of each week of treatment. Intact parathyroid hormone (PTH) levels decreased in both treatments, but there was no statistically significant difference between the treatments (**Table 2**). Serum alkaline phosphatase increased significantly with sevelamer treatment (86 ± 84 U/L to 114 ± 90 U/L, $p<0.0001$) and decreased insignificantly with calcium carbonate treatment (211 ± 88 U/L to 177 ± 79 U/L). Changes in the lipid profile with treatment are included in **Table 3**. When the patients ingested the sevelamer, they sustained a statistically insignificant decline in total cholesterol and triglycerides. However, there was an increase in cholesterol and triglycerides when they ingested the calcium carbonate.

Discussion. Phosphate removal with dialysis is practically poor.[8] The use of aluminum or calcium-based phosphate binders has been required for lowering serum phosphate levels in uremic patients.[9,10] Unfortunately, aluminum toxicity[11] and significant hypercalcemia[12] limit the usage of these agents. Hypercalcemia is especially problematic when calcitriol is administered in an attempt to modulate parathyroid hormone (PTH) levels.[13] Hypercalcemia not only causes unacceptable symptoms such as nausea and confusion,[14] but also results in an increase in the calcium-phosphate product with resultant arterial calcification.[15] Accordingly, sevelamer hydroxide, a novel calcium- and aluminum-free polymer, which forms ionic, and to a lesser extent hydrogen, bonds with phosphate may be a more ideal phosphate binder. This compound also binds bile acids, resulting in increased fecal bile acid excretion and a lowering of low-density lipoprotein (LDL) cholesterol.[16] Previous investigations have noted a reduction in serum phosphorus without the development of concurrent hypercalcemia in hemodialysis patients treated with sevelamer.[1,17] Furthermore, there was a cross-over comparative study with the standard therapy that confirmed the significantly decreased incidence of hypercalcemia in the sevelamer group.[2] These results were reproduced from many centers around the world, in humans[18-22] and animal models.[23] Our study shows similar findings of the effectiveness and safety of sevelamer in the Saudi chronic dialysis patients. Both sevelamer and calcium carbonate caused large reductions in serum phosphorus over the course of the study. A reduction in serum phosphorus was achieved over a similar time frame for both agents.

Patients were prone to develop hypercalcemia. Fifteen percent of patients were hypercalcemic during washout, and 56% developed significant hypercalcemia while receiving calcium carbonate. Others have noted a 15-30% prevalence of hypercalcemia in hemodialysis patients.[24,25] The markedly decreased incidence of hypercalcemia with sevelamer, occurring in only 15% of patients in this study, should allow for increased usage of

calcitriol and better modulation of PTH function. In addition, the need for more toxic aluminum-based binders (required because of hypercalcemia) may be eliminated with sevelamer. The higher percentage of patients of both arms of the study was most likely due to the fixed high concentration of the dialysate calcium concentration and the fixed calcitriol dose, which were not modulated during the both phases of the study.

Serum intact PTH levels decreased in both treatment groups, but there was no significant difference between both limbs of therapy. This is not unexpected, because serum calcium is an important modulator of PTH secretion and hyperplasia.[26,27] Furthermore, the hypophosphatemic effect of sevelamer decreases the stimulatory effect of phosphorus on PTH secretion. The increase in serum alkaline phosphatase during sevelamer treatment was likely attributable to its effect on bile acid metabolism, as one would expect a decrease in serum alkaline phosphatase from the bone with decreasing serum PTH levels. Other bile acid sequestrants, such as cholestyramine, have been associated with mild harmless elevations in serum alkaline phosphatase in the short and long term follow-ups.[28,29] Sevelamer has several attractive properties that could be very beneficial in lowering the rate of atherosclerosis in dialysis patients. Currently, atherosclerosis is accelerated by as much as 20 years in dialysis patients[30] compared with the general population, and cardiovascular disease accounts for the death of up to half of these patients.[31] Whereas, the relationship between LDL cholesterol and atherosclerosis in the end-stage renal disease population is difficult to determine (possibly due to the complicating effects of malnutrition on serum cholesterol and survival), there was a reported 27% reduction in cholesterol by sevelamer treatment (similar to the reduction obtained with traditional cholesterol-lowering agents[32,33]) that may potentially decrease atherosclerosis in dialysis patients.[2] In our study, there was a decrease in cholesterol and triglycerides with sevelamer of 13% in comparison with the 3% rise of both values when the patients were treated with calcium carbonate, but the difference was not statistically significant. This was due to the low baseline average of the lipids in the study patients. Perhaps even more important, sevelamer may decrease atherosclerosis in dialysis patients due to its effect on serum calcium and phosphate. Sevelamer decreases serum phosphorus concentration with little effect on serum calcium, resulting in an overall decrease in the serum calcium phosphate product. An increased calcium-phosphate product has been associated with increased aortic calcification in both uremic rats,[34] and long-term dialysis patients in 2 cross-sectional studies[34,35] and one longitudinal study.[30] Aortic and coronary artery calcification have also been found to be risk factors for cardiac events and death even in individuals without renal failure.[36-38] The use of sevelamer could potentially lower the calcium-phosphate precipitation and decrease calcification of the vasculature[39-42] The unique ability of a phosphate binder is not only to decrease serum phosphorus but also to improve serum cholesterol concentrations and it would be highly beneficial in the treatment of hemodialysis and chronic renal failure patients. Sevelamer and calcium carbonate were both well tolerated, and patients were approximately 88% compliant with each treatment. Whereas gastrointestinal adverse events were common with either treatment, they were often related to the dialysis procedure and did not result in differences in compliance between medications or differences in dropout rates. The longer-term follow-up studies of sevelamer usage in a larger number of patients have substantiated its safety.[4] The binding of phosphate and bile acids are both advantageous, however, the potential binding of other agents must be carefully studied. Both sevelamer and calcium carbonate are available for treatment of hyperphosphatemia. Sevelamer has potential advantages that include the ability to avoid hypercalcemia, decrease metastatic calcification and decrease serum cholesterol; in addition to deceased hospitalizations[43] and cost effectiveness in hyperlipidemic patients with hyperphosphatemia.[44] Hypocalcemia, which may lead to an increase in parathyroid hormone secretion, is less likely to occur with calcium carbonate. Both medications were well tolerated and without significant adverse effect during the study. Recent reviews of the strategies of the treatment of secondary hyperparathyroidism have favored the use of sevelamer in the high risk patients with tendency for hypercalcemia, those with significant vascular and non-vascular metastatic calcifications and those with need for lowering their cholesterol levels.[45-48]

In summary, sevelamer was very effective in lowering serum phosphorus concentrations in the Saudi hemodialysis patients, with a much lower incidence of hypercalcemia than calcium carbonate. Furthermore, sevelamer could significantly lower the serum calcium-phosphate product and serum cholesterol. The results of this study suggest that sevelamer can be of marked clinical utility in controlling serum phosphorus in the Saudi dialysis patients, especially those who are prone to hypercalcemia during the attempts to control their phosphorus.

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