

Sevelamer Hydrochloride: A new Approach to Hyperphosphatemia and Beneficial Effects Beyond Phosphate Control

João M. Frazão, Patrícia Martins, Carla Santos-Araújo

Nephrology Department, Hospital de S. João, Medical School of the University of Porto.
Nephrology Research and Development Unit, Porto, Portugal.

INTRODUCTION

Cardiovascular disease is a leading cause of death in the chronic kidney disease dialysis population. In this group of patients cardiovascular mortality is 20 times higher than in the general population^{1,2}. Although highly prevalent in the dialysis population, traditional risk factors such as diabetes and hypertension cannot account for such a high burden of cardiovascular events. There is very strong evidence indicating that disturbances of the mineral metabolism observed in patients with chronic kidney disease undergoing haemodialysis treatment, play an important role in the development of cardiovascular disease.

In recent years it has become clear that elevated serum phosphorus levels are positively associated with increased mortality^{3,4}. Hyper-

phosphatemia and elevated calcium-phosphorus product are associated with cardiovascular calcification^{5,6}, which is an independent predictor of mortality. Several authors have reported a strong positive association between the presence and extent of vascular calcification and both cardiovascular and all cause mortality^{7,8,9}. Raggi *et al*¹⁰ showed that previous myocardial infarction, angina and known coronary artery disease were all more common in patients with extensive calcification.

Hyperphosphatemia is highly prevalent in stage 5 chronic kidney disease patients. The clinical consequences include secondary hyperparathyroidism, with renal bone disease, extraosseous calcification and increased mortality.

Hyperphosphatemia plays an important role in the development of secondary hyperparathyroidism. Phosphorus has a direct effect on the

parathyroid gland stimulating the secretion of parathyroid hormone^{11,12} and also inducing resistance of the gland to the inhibitory effect of calcitriol.

It is very important to control phosphorus levels in the Chronic Kidney Disease (CKD) population. Therapeutic strategies to control it include dietary restrictions, dialysis, and the use of phosphate binding agents. Dietary control with reduction of phosphate intake is often difficult for patients to maintain and is limited by the inherent protein restriction. Phosphate is also difficult to remove by dialysis. Increased dialysis length or frequency may be effective, but it is often difficult to implement due to logistic problems and poor patient acceptance. Until recently, the only phosphate binders available were aluminium or calcium based compounds. Although efficacious they were associated with important side effects. The use of aluminium-containing phosphate binders may induce aluminium bone disease, as well as haematologic and central nervous system toxicity. The use of calcium-containing phosphate binders is associated with increased risk of hypercalcemia and cardiovascular calcification^{5,6,8,13}. It is now known that serum calcium levels are not accurate predictors of calcium balance and accumulation. The excessive amount of calcium ingested from the diet and from calcium-containing binders has been associated with cardiovascular calcification, even in the presence of recommended calcium serum levels^{5,6,8,13}. Sevelamer hydrochloride, the new non-calcium non-metal containing and only non-absorbed phosphate binder, provides an effective way to bind phosphorus in the gut without the risks of hypercalcemia, soft tissue and vascular calcifications, or heavy metal accumulation.

SEVELAMER HYDROCHLORIDE: CLINICAL DATA

Sevelamer is a cross-linked (allylamine hydrochloride) polymer. It contains multiple amines linked by a single carbon atom to a polymer backbone. Chemically, sevelamer is known as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane)hydrochloride. Sevelamer binds phosphate in the gut, preventing its systemic absorption. Except for a fraction of its chloride content that is displaced by phosphorus, the polymer is nonabsorbed. In the intestine, the amines within the sevelamer polymer become protonated and preferentially bind phosphate through ion exchange and hydrogen bonding to amino groups. The phosphate binding occurs mostly in the duodenum and its maximal binding activity is probably at a pH of 7.

Sevelamer hydrochloride has been widely studied and shown to be effective in reducing phosphorus levels and calcium-phosphorus product without causing hypercalcemia and soft tissue calcification in stage 5 CKD patients on haemodialysis. Moreover, sevelamer induces a reduction in total cholesterol and low density lipoprotein (LDL) cholesterol. With few side effects, this compound is very well tolerated. The more frequently reported adverse effects are diarrhoea, constipation, dyspepsia, nausea and vomiting.

An initial open label, randomized crossover study was performed to compare the efficacy and safety of this phosphate binder with calcium acetate¹⁴. After a two week washout period, 84 stable haemodialysis patients were started on either sevelamer or calcium acetate. The doses were titrated to achieve improved phosphate control over a period of 8 weeks. After two weeks of washout the patients were crossed over to the alternate phosphate binder. There was a similar and significant decrease in serum phospho-

rus levels with both compounds. Twenty two percent of the patients developed hypercalcemia, defined as a serum calcium level above 11 mg/dL, during treatment with calcium acetate, compared to a 5% incidence with sevelamer. The incidence of hypercalcemia during treatment with sevelamer was similar to the one seen during the washout period. Patients treated with sevelamer also experienced a significant and sustained decrease in serum LDL cholesterol levels (mean - 24%).

In a randomized, open-label study of 114 patients, long-term treatment with sevelamer was, for the first time, compared to calcium carbonate, the most commonly used calcium-containing binder in Europe¹⁵. Sevelamer effectively reduced serum phosphorus without the progressive cardiovascular calcification seen in the calcium carbonate treated patients. In this study sevelamer reduced serum phosphorus to a similar magnitude as calcium carbonate. However, calcium carbonate use was associated with a significant increase in serum calcium levels and more frequent episodes of hypercalcemia, when compared to sevelamer. Calcium carbonate also induced over-suppression of intact parathyroid hormone, with the majority of calcium-treated patients presenting levels below 150 pg/mL after 1 year. This occurred despite reductions in vitamin D use, dialysate calcium and binder dose in the calcium group, as per protocol indication. Patients on sevelamer required more binder when compared with patients on calcium carbonate, 5.9 g vs. 3.9 g per day, respectively. Patients on sevelamer experienced a significant reduction in total and LDL cholesterol compared to a nonchange in the calcium carbonate group. Coronary arteries and aorta calcifications were severe in both groups, at baseline. However, by electron beam computed tomography (EBCT) evaluation, the group of patients treated with calcium carbonate had

significant progression of coronary arteries and aorta calcifications after 26 and 52 weeks of treatment, compared to no alteration in the sevelamer-treated patients.

Chertow *et al*¹³ reported the results of a randomized parallel design clinical trial comparing sevelamer with the calcium-based phosphorus binders in 200 haemodialysis patients. Study outcomes included the targeted concentrations of serum phosphorus, calcium, and intact parathyroid hormone, as well as calcification of coronary arteries and thoracic aorta using an EBCT-derived score. Sevelamer and calcium-based compounds provided similar control of serum phosphorus (Fig 1) and calcium-phosphorus product. Compliance to the prescribed dose of binder in the sevelamer and the calcium groups was similar; 86 vs. 80%, respectively. The group treated with sevelamer received an average binder dose of 6.5 ± 2.9 g per day and the ones on calcium based binders 4.3 ± 1.9 g per day (4.6 g and 3.9 g per day of calcium acetate or calcium carbonate, respectively). The calcium-based group had more frequent episodes of hypercalcemia when compared to the sevelamer group 43% and 17%, respectively. Suppression of PTH below the 150 to 300 pg/ml range was more common at the end of the study in the calcium-based binders group, 57 vs. 30%, despite the protocol specified reduction or cessation of vitamin D for intact PTH below 150 pg/ml. Twelve percent of subjects in the calcium group required rescue therapy with aluminium containing binders for a calcium-phosphorus product above $72 \text{ mg}^2/\text{dL}^2$, compared to 4% of the patients in the sevelamer group. The total and LDL cholesterol decreased significantly in the sevelamer treated group compared to a nonchange in the calcium binders group. Of relevance, the EBCT performed at the beginning of the study detected a coronary artery calcification prevalence of 83% and aortic

calcification of 35% in the study population. There was a significant progression of the coronary artery and aortic calcification EBCT score at week 26 and 52 in the calcium-treated treated group, despite the use of an average dose of calcium-containing binders of only 4.3 ± 1.9 g per day. There was no significant progression in the sevelamer treated group (Fig 2). Routine biochemical safety parameters were similar between treatment groups, except for serum bicarbonate levels. The bicarbonate levels were slightly higher in the calcium-containing binders group, 22.1 ± 4.4 mEq/L, compared to the sevelamer group, 19.2 ± 4.3 mEq/L ($p=0.0003$), as calcium salts provide a base and sevelamer does not.

The clinical significance of this finding is still not very clear. Bommer J. *et al*⁶, studied the association of predialysis serum bicarbonate levels with mortality and hospitalization risk in the Dialysis Outcomes and Practice Patterns Study (DOPPS). This was an international, prospective and observational study of haemodialysis practices and associated outcomes. The midweek predialysis serum bicarbonate level averaged 21.9 mEq/l and correlated inversely with nPCR, serum albumin, and serum phosphorus values. Before and after adjusting for 15 comorbidities, nutrition, and equilibrated KT/V, a U-curve best represented the association between predialysis serum bicarbonate levels and the risk of mortality or hospitalization. Patients with midweek predialysis serum bicarbonate levels of 20.1 to 22.0 mEq/L had the lowest risk of mortality. The patients with serum bicarbonate levels of 21.1 to 22.0 mEq/L had the lowest risk of hospitalization. Levels of bicarbonate above 27 mEq/L and below 17 mEq/L were associated with increased risk of hospitalization and mortality.

The high prevalence of vascular calcification seen in the dialysis population in the Chertow

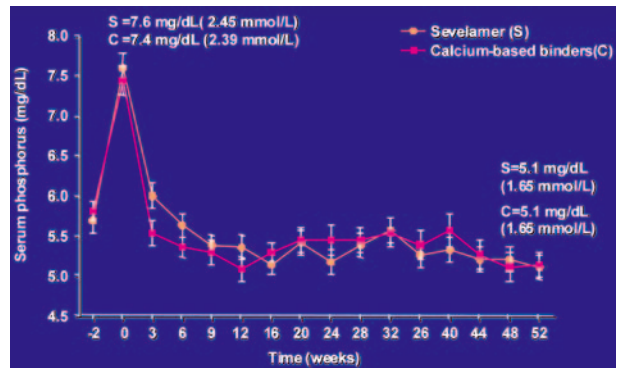


Figure 1. Serum phosphorus levels during 52 weeks of treatment with sevelamer versus calcium-based binders. Similar control of phosphorus levels was obtained in each group, a value below the K/DOQI recommended treatment target of 5.5 mg/dL. Data from reference 13.

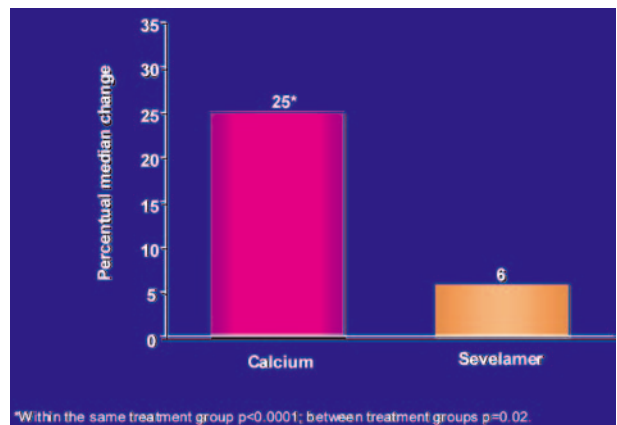


Figure 2. Median percentage change in coronary artery calcification scores obtained with EBCT scan at baseline and week 52 of treatment with sevelamer versus calcium-based binders. * Indicates within the same treatment group $p<0.0001$; between treatment groups $p=0.02$. Adapted from reference 13.

study¹³ has been confirmed by other reports and is of major concern due to the positive association between the presence and severity of calcification and mortality in this population. There is also some evidence that most of the patients develop vascular calcifications while on haemodialysis treatment. In fact, a report from Spiegel *et al*¹⁷ revealed that only 34% of patients with

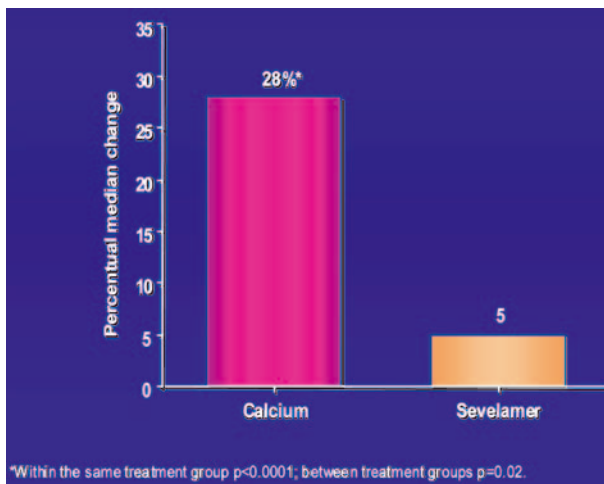


Figure 3. Median percentage change in aortic calcification scores obtained with EBCT scan at baseline and week 52 of treatment with sevelamer versus calcium-based binders. * Indicates within the same treatment group $p < 0.0001$; between treatment groups $p = 0.02$. Adapted from reference 13.

advanced chronic kidney disease starting dialysis had coronary artery calcifications scores that placed them above the 90th percentile for age and sex. In this patient population initiating dialysis, 109 patients underwent baseline and at least one additional measurement of coronary artery calcification¹⁸. At baseline, 37 % of the patients that underwent treatment with sevelamer and 31% of the patients on calcium-based binders had no evidence of calcification. The authors reported that no patients with a zero coronary calcium EBCT score progressed to > 30 , in a 18 months period of time. Patients with a coronary artery calcium score already over > 30 at baseline, progressed in both arms during the time of the study. Patients treated with calcium-based binders showed a more rapid and severe progression of calcification scores when compared to the ones receiving sevelamer. It is noteworthy that during this study all the patients were maintained on dialysis with a calcium dialysate concentration of 2.5 mEq/l. The authors con-

cluded that patients new to dialysis with no evidence of coronary calcification showed little evidence of disease development over a period of 18 months independently of the phosphate binder used. Patients with even little evidence of coronary calcification progressed with both binders, however, the group treated with calcium had a much more pronounced progression when compared to the patients treated with sevelamer¹⁸. This study, which has just been published, is no doubt confirming the importance of the K/DOQI clinical practice guideline for bone metabolism and disease in CKD which recommends that calcium-based binders should be avoided in patients with evidence of severe calcification.

Serum concentration of C-reactive protein (CRP), a non-specific marker of inflammation, is predictive of coronary artery disease events in the general population¹⁹ and has also been shown to be associated with an unfavourable outcome in stage 5 CKD populations on haemodialysis^{20,21}. Statin treatment to reduce LDL cholesterol decrease coronary artery events and serum CRP²², suggesting a possible relationship between lipoprotein infiltration of the vessel wall and the inflammatory process. Similar mechanisms may be important in the dialysis population. Sevelamer treatment has been shown to reduce total and LDL cholesterol. A recently published study compared the effect of sevelamer and calcium carbonate on serum lipoproteins, homocysteine, and markers of inflammation such as $\beta 2$ -microglobulin and high-sensitivity CRP protein, as well as progression of arterial calcification²³. After 1 year of treatment the calcium score progressed from baseline in the calcium acetate treated group compared to a non-change in the sevelamer group. Total and LDL cholesterol, apolipoprotein b, $\beta 2$ -microglobulin, and high-sensitivity CRP protein decreased significantly from the baseline values

in the sevelamer treated group compared to a no alteration in the calcium acetate patients, despite the more frequent use of statins in the latter. These data confirm that sevelamer has favourable effects in lipids, but also suggest a positive action in the inflammatory markers with potentially useful antiatherogenic effects in the haemodialysis population. In another randomized clinical trial comparing sevelamer and calcium-based phosphate binders, treatment with sevelamer was associated with a significant reduction in the serum uric acid levels²⁴.

A posthoc analysis of a 52 week randomized trial conducted in adult haemodialysis patients evaluated the effect of calcium-based binders and sevelamer on thoracic vertebral attenuation by computed tomography and markers of bone turnover²⁵. When compared to the ones treated with sevelamer, subjects randomized to calcium salts experienced a significant reduction in trabecular bone attenuation and a trend towards reduction in cortical bone attenuation, in association with higher concentrations of serum calcium, lower PTH values, as well as, reduced total and bone-specific alkaline phosphatase. These results suggest that the use of calcium salts to treat hyperphosphatemia may paradoxically decrease bone mineral density in haemodialysis patients.

In a case-controlled study of 152 Medicare haemodialysis patients, Collins *et al*⁶ showed that the benefits of treatment with sevelamer may result in a decreased number of hospitalizations. In this analysis, the risk of hospitalization was, in fact, 46-54% less in patients treated with sevelamer compared with a matching control group. This reduced risk was primarily due to the lower incidence of hospitalizations due to cardiovascular and vascular access complications.

A three-year trial involving more than 2,100 patients, the largest outcomes study ever con-

ducted in the haemodialysis population, has just been communicated (Genzyme CO press release, July 28, 2005): this study compared the difference in mortality and morbidity outcomes for patients receiving sevelamer and those on calcium-containing phosphate binders. It showed that the patients treated with sevelamer experienced a reduction of 9 percent in the risk of death from all causes when compared to patients treated with calcium-based phosphate binders, but this value didn't reach statistical significance ($p=0.3$). However, patients aged 65 years old or more were 22 % less likely to die when treated with sevelamer, compared to the treatment with calcium-based binders. Moreover, patients on sevelamer for more than two years had a 34% reduction of the risk of mortality from all causes compared to those treated with calcium-containing binders. Patients of 65 years old or more, who were treated with sevelamer for over two years, presented a mortality risk reduction of 54% when compared to the ones treated with calcium-containing compounds.

The current National Kidney Foundation K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease²⁷ state clearly that clinical use of sevelamer is recommended as an important first-line treatment option for the control of hyperphosphatemia and/or an elevated CaxP product in stage 5 CKD patients. The use of calcium from phosphate binders is recommended to be limited to 1.5 g of elemental calcium per day. Given the most recent evidence of calcification progression with similar quantities of calcium¹³, this value could be decreased in a future revision of this recommendation. Patients with hypercalcemia (corrected serum calcium > 10.2 mg/dL), or with plasma intact PTH levels below 150 pg/mL on two consecutive measurements, or with severe vascular calcification and/or other soft tissue calcification, should also be treated with sevelamer

as a phosphate binder. These recommendations were very much in line with the available data at the time but perhaps in view of all the data here presented they should be soon revised to include even a larger universe of haemodialysis patients for treatment with sevelamer.

Sevelamer, a cross-linked, non-absorbed, calcium and metal-free polymer, effectively reduces phosphorus levels, in the haemodialysis population without the burden of hypercalcemia or calcium load. Sevelamer is associated with a beneficial effect in lipid profile, inducing reductions in the total and LDL cholesterol. The positive effect of reducing CRP levels - an inflammatory marker - has also been observed with the use of this compound. When compared to calcium-based binders, sevelamer slows coronary artery and aortic calcification progression. Of most importance is yet the upcoming evidence of the association between sevelamer use and reduction of mortality and morbidity in the dialysis population. Sevelamer hydrochloride has become the standard of care in hyperphosphatemia control, with beneficial effects undoubtedly surpassing phosphate management.

Correspondence:

Prof. Doutor João Miguel Frazão
Hospital de S. João, Serviço de Nefrologia
Alameda Hernâni Monteiro
4200 Porto - Portugal

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