Sevelamer hydrochloride: a calcium- and metal-free phosphate binder

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Sevelamer hydrochloride is a nonabsorbed, calcium- and metal-free phosphate binder, used to bind phosphate and prevent phosphate accumulation in patients with kidney failure. Sevelamer hydrochloride has been an important alternative to calcium-based phosphate binders, because calcium-based binders result in increased gastrointestinal calcium absorption and a positive calcium burden in dialysis patients. Recent studies have shown that sevelamer hydrochloride slows the progression of cardiovascular calcification when compared with calcium-based binders – such decreases in cardiovascular calcification may potentially lead to a reduction in morbidity and mortality in dialysis patients.

Keywords: aluminum hydroxide, cardiovascular calcification, chronic kidney disease, hyperphosphatemia, lanthanum carbonate, phosphate binders, sevelamer hydrochloride.

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Chronic kidney disease (CKD) is characterized by high morbidity and mortality rates [1,2], and is accompanied by abnormalities of mineral metabolism such as hyperphosphatemia and calcium imbalances. Hyperphosphatemia develops when the intake of phosphorus from the diet and the efflux of phosphorus from bone or other cellular stores, exceeds the amount that can be excreted by the diseased kidneys and removed by tissue uptake. Since much of phosphorus is intracellular, it is not easily removed by dialysis. In patients with kidney failure, dietary phosphorus restriction is employed, but phosphorus intake in the diet cannot be avoided due to the need for consumption of protein, which contains phosphorus. Moreover, young patients with healthy appetites will find it very difficult to strictly follow low phosphorus diet recommendations [3–6]. Most patients are therefore in positive phosphorus balance [7] and require a phosphate-binding agent to reduce phosphorus absorption in the intestine [8,9]. Of note, daily hemodialysis is gaining popularity in the USA, although this treatment still constitutes only a fraction of the patients on dialysis. Patients who receive daily hemodialysis have markedly improved phosphorus control, and many of these patients have a normal serum phosphorus level even after ceasing all phosphate binders [10].

Hyperphosphatemia is an important risk factor for the development of serious complications such as cardiovascular disease [11–13] – the leading cause of death among CKD patients [2]. The mortality rate rises in tandem with the serum phosphorus concentration [4,11,12,14–16]. It has been postulated that improvements in patient survival could be achieved by maintaining the serum phosphorus concentration below 5.5 mg/dl [17]. Hyperphosphatemia also plays a critical role in the development of secondary hyperparathyroidism and renal osteodystrophy [5,18–22], and may contribute to kidney failure progression [23].

Calcium imbalances are another mineral derangement commonly seen in CKD. Excess calcium load is a particular problem in dialysis patients because hemodialysis and peritoneal dialysis regimens are not designed to remove calcium effectively. In addition, vitamin D analogues are commonly given to patients on dialysis, resulting in increased intestinal calcium absorption. This situation is further compounded by the very large calcium load contributed by calcium-based phosphate-binding agents. Excess calcium loading contributes to soft-tissue and cardiovascular calcification, an active process that resembles bone formation biochemically [21,24–30]. Furthermore, cardiovascular calcification has adverse effects on cardiac function [25,31] and increases the risk of death [31].

The importance of proper mineral balance in hemodialysis patients is emphasized by the recent findings by Block and colleagues, which demonstrated that the mortality risk associated with mineral metabolism disorders is greater than that attributable to either anemia or inadequate dialysis [15]. Their data showed that calcium–phosphorus (Ca × P) products above 50 mg^2/dl^2 are associated with an increased relative risk of death, and both serum phosphorus concentrations above 5.0 mg/dl and serum calcium concentrations above 9.5 mg/dl are significantly and independently associated with an increased relative risk of death [15]. Current National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) Guidelines recommend maintaining serum

phosphorus concentrations between 3.5 and 5.5 mg/dl, and serum calcium concentrations within the normal range, preferably between 8.4 and 9.5 mg/dl [32].

Overview of the market

Traditional phosphate binders include calcium acetate, calcium carbonate and calcium citrate [20]. These binders can control serum phosphorus [32], resulting in a decrease in parathyroid hormone (PTH) levels [33], and are relatively inexpensive [34]. However, they are a major contributor to excess calcium load in dialysis patients [35,36] and are associated with significant, progressive vascular calcification and arterial stiffening [34,37–42]. Both chronic excess calcium load and hypercalcemia encourage calcification of the cardiovascular system [9,26,33,39,40,43–45], which stiffens the arteries [25] and has adverse effects on patient health [24,25,31]. Indeed, severity of arterial calcification is a strong predictor of mortality in hemodialysis patients [46,47]. Use of calcium-containing phosphate binders is associated with relatively rapid progression of vascular calcification, despite the maintenance of serum phosphorus, calcium and calcium–phosphate product levels within the normal range in most patients [39,40].

Calcium-based phosphate binders may also encourage widespread calcification of other soft tissues, most severely as calcific uremic arteriolopathy (CUA; calciphylaxis) [5,25,48]. Excess calcium load and subsequent suppression of PTH are also associated with a low turnover bone state and adynamic bone disease, which are likewise increasing in incidence [22]. Owing to the above concerns, the NKF has issued guidelines for the use of phosphate binders in renal failure. These guidelines are not simply perfunctory, but are actively read and used by a high number of practicing nephrologists in the USA and globally. The NKF recommends restricting the total intake of elemental calcium to no more than 2000 mg/day and the elemental calcium intake from phosphate binders to no more than 1500 mg/day. When the total serum calcium concentration exceeds 10.2 mg/dl, calcium-containing phosphate binders should be reduced or eliminated [32]. A large number of patients will not achieve adequate phosphate restriction when only calcium-based phosphate binders are used and limited to providing 1500 mg elemental calcium/day.

The goal of phosphate-binder therapy is to effectively control serum phosphate levels without complicating other areas of mineral balance. There is a need for safe and effective phosphate binders that will not add to the calcium load. Currently, two calcium-free options are commonly used as phosphate binders – sevelamer hydrochloride (sevelamer) and lanthanum carbonate (lanthanum).

The US Food and Drug Administration (FDA) gave marketing clearance to lanthanum as a phosphate binder late in 2004. Lanthanum is supplied in chewable tablets, with one tablet containing 500 mg of lanthanum carbonate and weighing approximately 3600 mg.

Early clinical trials suggest that lanthanum is both effective and safe [49–53]. Given past concerns about aluminum deposition in patients with kidney failure receiving aluminum-based binders, attention has been directed at any potential clinical toxicity from lanthanum. No evidence of such toxicity has been demonstrated in clinical trials and the compound has been noted to be an effective phosphate binder [52]. A major concern has been whether lanthanum will result in osteomalacia as has previously been noted with the phosphate binder aluminum hydroxide. This has proven not to be the case. A multicenter, randomized open-label study of lanthanum in 98 patients, with bone biopsies performed 1 year apart, assessed the effect of lanthanum on bone formation [49]. In 49 patients randomized to lanthanum, the number of patients with either adynamic bone disease, osteomalacia or hyperparathyroid bone disease decreased from 12 to six patients. In contrast, in the calcium carbonate group, the number of patients increased from 13 to 16 [54]. Six patients in the calcium carbonate group developed adynamic bone disease. Therefore, patients randomized to lanthanum showed improvements in renal osteodystrophy relative to calcium. In a study of 11 patients receiving lanthanum for more than 4 years, there was no evidence of osteomalacia on bone biopsy [53].

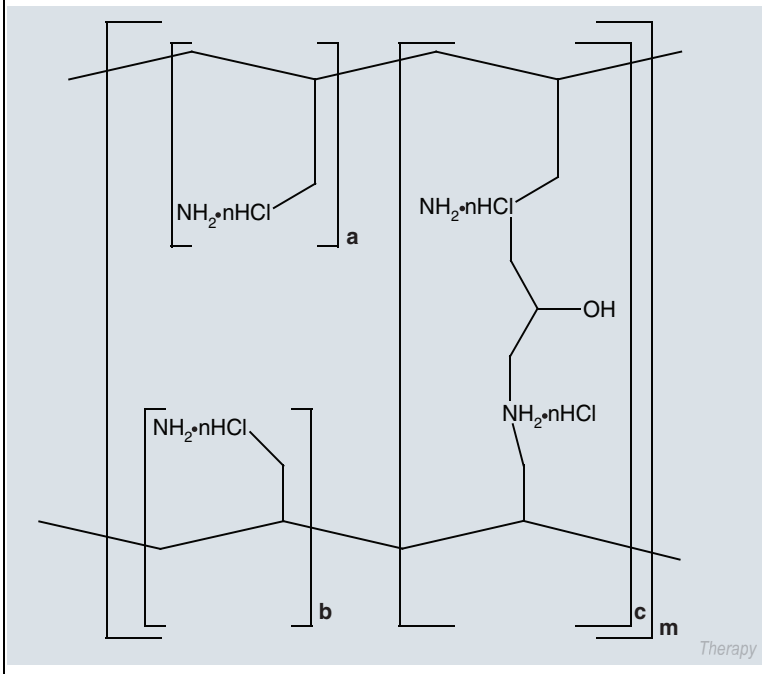
Sevelamer is a recently introduced, calcium- and metal-free phosphate binder with demonstrated efficacy [55–58]. Substituting sevelamer for calcium-based phosphate binders markedly decreases the total calcium load to within NKF guidelines [35,36,40].

Introduction to the compound

Chemistry

Sevelamer is a cationic hydrophilic hydrogel that expands, but is insoluble in water. The compound consists of a poly(allylamine hydrochloride) cross-linked with epichlorohydrin in which

Figure 1. Chemical structure of sevelamer.



a, b: number of primary amine groups (a + b = 9); c: number of crosslinking groups (c = 1); n: fraction of protonated amines (n = 0.4); m: large number to indicate extended polymer network.

40% of the amines are protonated. The chemical name is poly(allylamine-co-*N*,*N*′-diallyl-1,3-diamino-2-hydroxypropane) hydrochloride (**Figure 1**).

At neutral pH, sevelamer readily binds the oxygen atoms of phosphate [59,60]. At a physiologic phosphate concentration of 5 mM, the binding capacity is 2.6 mmol phosphate/g of phosphate binder [61]. Dianions, such as phosphate are bound in preference to monoanions, such as bicarbonate and chloride.

Sevelamer has a high capacity for binding bile acids [62], thus increasing their fecal excretion. This property is consistent with the observation in numerous studies that sevelamer reduces serum levels of low-density lipoprotein (LDL) cholesterol [36,56–58].

Pharmacokinetics

Rats that received single oral doses of [^{3}H]sevelamer had no significant excretion of radioactivity in their urine – 98% of radioactivity was recovered in the feces. In rats that were pretreated with the unlabeled drug for 28 days before receiving a single oral dose of [^{3}H]sevelamer, fecal recovery was near 100% – a total of less than 0.1% of the dose was found in the tissues [63]. Following 28 days of pretreatment with the unlabelled sevelamer, administration of single ^{14}C-sevelamer doses to human volunteers resulted in no recovery of the isotope from the blood. Most subjects had no ^{14}C recovered in the urine and, in those subjects with detectable ^{14}C in the urine, the amount was less than 0.02% of the dose. More than 99% of the ^{14}C dose was recovered in the feces. These findings demonstrate that the compound is not absorbed [63]. No similar absorption studies have been conducted in patients with stage 5 CKD.

Preclinical & animal studies

In rats fed sevelamer at various concentrations for 4 days, urinary phosphorus excretion declined in a dose-dependent fashion [61]. Particles with a mean diameter of 23 µm were the most efficacious [61]. Rats with doxorubicin-induced renal insufficiency were fed diets consisting of 1 or 3% sevelamer for 84 days. Sevelamer treatment prevented the occurrence of hyperphosphatemia, and elevations in Ca × P product and PTH concentrations without changes in serum calcium levels [64]. In rats with induced renal insufficiency, the feeding of 1 or 3% sevelamer resulted in reduced elevation of serum phosphorus, Ca × P product and PTH levels, and less parathyroid gland hyperplasia than in animals not receiving the drug [65–67]. Uremic rats given sevelamer had lower serum phosphorus, Ca × P product and PTH levels than uremic control animals [68–70]. Sevelamer prevents the development of renal osteodystrophy [70].

Uremic rats treated with sevelamer had less aortic calcification than uremic control animals [70], and less cardiovascular [69] and renal calcification [68,69] than both uremic controls and uremic animals treated with calcium carbonate. Preliminary data (published in abstract form) showed that uremic apoE-/- mice receiving sevelamer demonstrated less vascular calcification and progression of atherosclerosis than uremic control animals and uremic animals given calcium carbonate [71].

Clinical efficacy

Control of serum phosphate levels

Numerous studies have shown sevelamer effectively reduces serum phosphate levels [56,72,73]. An 8-week randomized double-blind trial comparing sevelamer with calcium carbonate/calcium acetate was carried out in 36 hemodialysis patients [74]. Within 2 weeks, sevelamer produced a significantly greater decline in serum phosphorus (from 6.6 ± 2.1 to 5.4 ± 1.5 mg/dl) than did placebo (from 7.0 ± 2.2 to

7.2 ± 2.4 mg/dl; p = 0.037). There was no significant change in the serum calcium concentration in either group [74].

Another 8-week open-label dose-titration study involved 172 hemodialysis patients with mean serum phosphorus concentrations of 9.1 ± 2.4 mg/dl after a 2-week washout from all phosphate binders [57]. At the end of the 8 weeks, the average daily dose of sevelamer was 5.4 g. The mean serum phosphorus concentration declined to 6.6 ± 1.9 mg/dl (p < 0.0001) while the average serum calcium concentration rose by a mean of 0.3 mg/dl (p < 0.0001) [57].

An 8-week open-label dose-titration crossover comparison of sevelamer and calcium acetate was carried out in 84 hemodialysis patients with a 2-week washout period between the treatments [36]. The serum phosphorus concentration declined to a similar extent with the two agents (sevelamer: -2.0 ± 2.3 mg/dl; calcium acetate: -2.1 ± 1.9 mg/dl). Hypercalcemia (serum calcium > 11.0 mg/dl) was detected in 5% of the patients during sevelamer administration compared with 22% during calcium acetate administration (p < 0.01) [36].

In the 8-week Calcium Acetate Renagel Evaluation (CARE) trial, 100 hemodialysis patients were randomized to receive either calcium acetate or sevelamer [75,76]. In this study, the mean dose of calcium acetate used was higher than that of sevelamer for the majority of the study. This protocol resulted in the sevelamer group being underdosed for most of the 8-week study and reaching an effective dose at a much later point in the trial than the calcium group. Patients taking calcium acetate had a serum phosphorus concentration averaging 1.08 mg/dl lower than those taking sevelamer (p = 0.0006), a higher serum calcium concentration (average difference 0.63 mg/dl; p < 0.0001), and a Ca × P product that was lower by an average of 6.1 mg^2/dl^2; p = 0.022) [75,76].

In a 5-month randomized open-label study, 42 patients were randomized to continue taking calcium acetate at an average dose of 4.8 g/day or to change to sevelamer in a dose averaging 4.4 g/day [77]. If the serum calcium concentration was less than 9.2 mg/dl, either the dialysate calcium concentration was increased or α-calcidol was given. During the first month, serum phosphate concentrations in the sevelamer group showed a show transient increase over the the calcium acetate-treated baseline – however this was not observed in the subsequent months. The serum bicarbonate concentration showed a small transient decrease in the sevelamer group compared with the calcium carbonate-treated group in the second month only [77].

A 36-week randomized study of sevelamer and calcium acetate involved 40 patients who had a serum phosphorus concentration of 6 mg/dl or more after a 2-week washout period [78]. The mean daily dose of sevelamer was 4.09 g whilst that of calcium acetate was 3.9 g. In patients receiving sevelamer, the mean serum phosphorus concentration declined from 8.09 ± 1.6 mg/dl to 5.8 ± 1.01 ng/dl (p = 0.001). In patients receiving calcium acetate the decline was from 7.5 ± 1.6 mg/dl to 5.9 ± 1.5 mg/dl (p = 0.005). Although there was no significant increase in the mean calcium concentration in either group, at least one episode of hypercalcemia (serum calcium > 11.0 mg/dl) occurred in both groups of patients (7.1% of the sevelamer group and 8.9% of the calcium acetate group; p = 0.2). The mean change in Ca × P was similar in the two groups [78].

Dialysis patients (n = 192) from earlier trials [36,72,74] were enrolled in a long-term (46-week) open-label trial of sevelamer at a mean daily dose of 5.3 g [58]. The mean decline in serum phosphorus was 2.20 ± 2.38 mg/dl (p < 0.0001) and there was a slight mean increase in serum calcium of 0.32 ± 0.88 mg/dl (p < 0.0001). The Ca × P product declined an average of 18.0 ± 22.0 mg^2/dl^2 (p < 0.0001) [58]. A follow-up analysis showed that at 2 years, the Medicare patients from this series who had been randomized to sevelamer were 46 to 54% less likely to require hospitalization than patients using other phosphate binders (p = 0.03) [79].

An open-label randomized 52-week trial was carried out in 223 hemodialysis patients [80]. After a 2-week washout period, patients took either sevelamer or calcium salts (acetate or carbonate) for a 12-week dose-titration period and then for 40 weeks, during which time further binder-dose adjustments and optimization of the doses of vitamin D and other drugs was 'encouraged'. The mean serum phosphorus concentration remained close to the target (3.0–5.0 mg/dl) in both groups (5.2 mg/dl with sevelamer, and 5.1 mg/dl with calcium salts). Hypercalcemic episodes (serum calcium concentration > 1.0 mg/dl) were more common in patients taking calcium salts (33 vs. 7%) [80].

A trial of sevelamer as a supplement to calcium-containing phosphate binders was conducted in 23 hemodialysis patients with a serum calcium

concentration of more than 10.4 mg/dl [81]. Initially, half of the calcium-containing binder dose was replaced with sevelamer. If serum calcium remained elevated after 4 weeks, half of the remaining calcium-containing binder dose was replaced with sevelamer. If serum phosphorus remained over 6.2 mg/dl, the sevelamer dose was increased by 25%. Patients were then followed for an additional 4 weeks. The eventual mean daily sevelamer dose was 2.77 ± 0.37 g, which is considerably lower than most other studies. The mean daily elemental calcium dose declined from 2.05 ± 0.23 to 1.03 ± 0.1 g. The mean serum phosphorus concentration was stable. The percentage of patients who were hypercalcemic declined from 100 to 26%, with the mean serum calcium falling from 11.2 ± 0.16 mg/dl to 10.2 ± 0.12 mg/dl ($p < 0.0005$) [81].

Effects on cardiovascular calcification & mortality

Several studies have shown sevelamer attenuates the progression of cardiovascular calcification in chronic hemodialysis patients [39,82–84]. Two case reports describe CUA lesion resolution with treatment that included substituting sevelamer for calcium-containing phosphate binders [48,85].

The Treat-to-Goal study was the most important study to demonstrate that sevelamer attenuates the progression of cardiovascular calcification, while calcium-based phosphate-binders promote calcification [39,83]. This is the first phosphate binder study performed in dialysis patients that looked at an end point besides control of serum calcium and phosphorus values, and actually assessed long-term clinical benefits that can be derived from phosphorus binders. In the Treat-to-Goal study, a randomized open-label trial, hemodialysis patients (n = 200) were examined by electron-beam tomography (EBT) at baseline and after 1 year of treatment, to determine whether replacement of calcium-containing binders by sevelamer affected the rate of progression of vascular calcification [39,83]. In the entire series of patients, the amount of calcification at baseline directly correlated with the likelihood and extent of progression over time. The median absolute coronary and aortic calcium scores increased significantly in the patients taking the calcium-containing phosphate binders, but not in those receiving sevelamer. The median percent change in calcium score was significantly greater in patients receiving calcium-based phosphate binders than in patients receiving sevelamer (coronary artery score: 25 vs. 6%; $p = 0.02$; aortic score: 28 vs. 5%; $p = 0.02$). The differences in calcification between groups were accentuated among patients with greater baseline calcification. When the database was analyzed to determine whether there was a difference in the effects of calcium acetate and calcium carbonate, no difference was found [40].

Valvular calcification was also assessed in the Treat-to-Goal study [39,84]. At baseline, 46% of the subjects had mitral valve calcification and 33% had aortic valve calcification. Aortic valve calcification increased significantly only in patients receiving a calcium-containing phosphate binder. Changes in mitral and mitral + aortic valve calcification were less in the sevelamer-treated patients, although the difference was not statistically significant. The change in valvular + vascular calcification was significantly less in the sevelamer-treated patients. This effect remained significant after adjustment for the baseline calcium score and the time-averaged Ca × P product. More sevelamer- than calcium-treated patients had the extent of their total valvular + vascular calcification remain stable (45 vs. 28%; $p = 0.047$) or regress (26 vs. 10%; $p = 0.02$) [84].

In an independent 52-week comparison of calcium carbonate and sevelamer, patients receiving the former had a median 34% increase ($p < 0.01$) in coronary artery calcification and a median increase of 32% ($p < 0.01$) in aortic calcification, whereas no progression of coronary artery calcification and significant regression of aortic calcification was observed with sevelamer [82].

In view of the increased risk of vascular soft-tissue calcification in patients receiving calcium-containing phosphate binders, it is now generally recommended that individuals with calciphylaxis (CUA) be treated with noncalcium-containing binders such as sevelamer to decrease calcium load and hopefully aid in the healing of these lesions [48,85].

Cardiac deaths were studied in patients who had received sevelamer (n = 696), calcium carbonate (n = 3279) or calcium acetate (n = 4018) for at least 1 year [86]. Cardiac deaths were significantly less common in patients receiving sevelamer than in patients taking calcium acetate (10.8 vs. 16.6%; $p < 0.001$) but there was no significant difference between patients taking sevelamer and those receiving calcium carbonate (12.6%) [86].

Effects on serum lipids

Numerous studies have shown that serum total and LDL cholesterol decline significantly during treatment with sevelamer [55–58].

Sevelamer treatment for 8 days in healthy subjects reduced the total serum cholesterol by an average of 27.5, 21.3 and 41.8 mg/dl, at daily doses of 1, 2.5 or 5 g respectively [55]. The serum total cholesterol declined an average of 25 mg/dl (176–149 mg/dl, a 14% decrease; p = 0.0001) and the LDL cholesterol declined an average of 23 mg/dl (98–73 mg/dl, a 23% decrease; p = 0.0001) during 8 weeks of sevelamer treatment [56]. In another study, after 8 weeks of treatment with sevelamer, the mean total cholesterol declined from 171.0 ± 43.1 mg/dl to 145.0 ± 38.7 mg/dl and the mean LDL cholesterol from 102.0 ± 34.9 to 75.6 ± 29.4 mg/dl (both: p < 0.0001) [57]. Another set of patients receiving sevelamer for 8 weeks demonstrated significant reductions in serum total cholesterol (p = 0.013) and LDL cholesterol (p = 0.003), compared with patients receiving calcium carbonate or acetate [74]. In another 8-week study, serum total cholesterol declined an average of 23.0% and serum LDL cholesterol decreased an average of 35.9% during sevelamer treatment (p < 0.02 for both), while there were no changes in high-density lipoprotein (HDL) cholesterol or triglycerides [73]. In an open-label, randomized, crossover study of adult hemodialysis patients, there was a mean decline of 24% in LDL cholesterol during 8 weeks of sevelamer treatment [36]. A 12-week study of sevelamer in hemodialysis patients with severe secondary hyperparathyroidism found a mean decline of 35 ± 10 mg/dl in the LDL cholesterol concentration (p < 0.01) [87].

The serum LDL cholesterol concentration reduced by 18% after 5 months of sevelamer treatment (p < 0.02) and was significantly lower than in patients who had received calcium carbonate for 5 months (p < 0.02) [77]. Serum lipid values did not change during a 6-month study of sevelamer in children and adolescents receiving peritoneal dialysis or hemodialysis [88]. In a 6-month study in adult hemodialysis patients where sevelamer was added to the current phosphate binder regimen, both total cholesterol (p < 0.01) and LDL cholesterol (p < 0.03) declined significantly [89].

A 36-week randomized comparison of sevelamer and calcium acetate was conducted [78]. The sevelamer group had a mean decline of 16.5% in serum total cholesterol and 29.9% in LDL cholesterol, while serum HDL cholesterol concentration increased an average of 19.5% (p < 0.05 for all values) – no significant changes were seen in the calcium acetate group [78]. During a 46-week open-label study of dialysis patients treated with sevelamer at a mean daily dose of 5.3 g, the serum LDL cholesterol concentration declined an average of 30%, while the mean HDL cholesterol rose an average of 18% (p < 0.0001 for both) [58].

In a 52-week open-label randomized study, serum LDL cholesterol declined significantly in patients taking sevelamer [80]. Significant reductions (p < 0.01) in total (24%) and LDL cholesterol (30%) were seen in patients receiving sevelamer for 52 weeks [82]. In another 1-year study, patients treated with sevelamer had significant decreases in serum total cholesterol (from 188–164 mg/dl; p = 0.005) beginning in the first week of treatment, with no changes being seen in HDL or LDL cholesterol levels [90].

In general, the effect of lowering serum cholesterol on cardiovascular morbidity and mortality in dialysis patients is unknown, as cardiovascular mortality is high in this population, despite the presence of a low serum cholesterol (due to anorexia and poor nutritional intake) in many dialysis patients, and serum cholesterol has not been found to be a consistent predictor of survival in dialysis patients.

Effects on parathyroid hormone & bone

Sevelamer treatment is associated with variable effects on PTH [36,56–58] depending on concurrent treatment factors. It has also been associated with a significant increase in trabecular bone density [42].

The serum intact PTH (iPTH) concentration declined from 395 pg/ml after a 2-week washout period, to a median of 283 pg/ml after 6 weeks of sevelamer treatment [56]. After 8 weeks of sevelamer treatment, the mean serum iPTH concentration declined from 316 to 224 pg/ml (p < 0.0001) [57]. The serum iPTH concentration declined significantly (p < 0.05) during 8 weeks of sevelamer treatment [73]. During 8 weeks of sevelamer treatment, serum iPTH levels declined by 48.2 ± 168 pg/ml (p < 0.05) [36]. In the 8-week CARE trial, serum iPTH concentrations were not significantly different between groups receiving calcium acetate or sevelamer [75,76]. In a different 8-week study where sevelamer was added to the current calcium-containing phosphate-binder regimen, the serum iPTH concentration increased significantly (166 ± 47 to 276 ± 104 ng/l; p = 0.02) [81].

Sevelamer efficacy was studied in 55 hemodialysis patients randomized to receive sevelamer for 12 weeks with or without supplemental calcium [72]. The reduction in serum PTH was

greater in the patients who received sevelamer plus supplemental calcium (-67 vs. -22.5 pg/ml; p = 0.07). The difference was particularly pronounced in patients who did not receive vitamin D (-114.5 vs -22 pg/ml; p = 0.006) [72]. In another 12-week study of sevelamer in hemodialysis patients with severe secondary hyperparathyroidism, serum iPTH remained stable [87].

In patients receiving either calcium carbonate or sevelamer for 5 months, serum PTH rose and 25-OH vitamin D declined significantly. The values of these two parameters were inversely correlated [77]. Serum PTH values did not change during a 6-month study of sevelamer in children and adolescents receiving peritoneal dialysis or hemodialysis [88]. In a 36-week randomized comparison of sevelamer and calcium acetate, serum iPTH concentration decreased from 479 ± 288 to 330 ± 205 pg/ml (p = 0.04) in the sevelamer group and from 501 ± 303 to 346 ± 250 pg/ml (p = 0.02) in the calcium acetate group [78]. In a 46-week study of sevelamer in dialysis patients there were no significant changes in serum PTH [58].

In an open-label 52-week study, patients receiving sevelamer were more likely to achieve the target serum iPTH value of 150 to 300 pg/ml than patients receiving calcium salt [80]. Serum iPTH was suppressed to an undesirable extent (<150 pg/ml) in approximately half the patients taking calcium salts despite reductions in vitamin D dose and dialysate calcium concentration in some patients [80].

A 52-week open-label trial compared sevelamer alone, sevelamer with vitamin D metabolites with or without calcium and sevelamer plus calcium without vitamin D [91]. Only the subjects who also received vitamin D metabolites had a decline in serum PTH – the other groups had an increase in serum PTH levels. The investigators concluded that sevelamer should be given in conjunction with vitamin D to control both hyperphosphatemia and hyperparathyroidism [91].

Analysis of computerized tomograghy scans after 2 years, showed a significant increase in trabecular bone density and a nonsignificant increase in cortical bone density in the sevelamer-treated patients, compared with a significant decrease in trabecular bone density and a nonsignificant decrease in cortical bone density in patients receiving calcium-containing phosphate binders [42]. Initial evidence suggests that the excess calcium provided by binders does not increase, but rather decreases, bone mineral density [92].

Safety & tolerability

Overall, sevelamer is safe and generally well tolerated, with no dose-related increases in adverse events related to treatment. The most prevalent adverse events in patients given sevelamer are gastrointestinal, with nausea being the most common and fewer patients reporting constipation, diarrhea, flatulence and/or dyspepsia [39,81,89,93]. These adverse effects are similar to those seen in all phosphate binders used in dialysis patients.

Serum bicarbonate concentrations may be lower during sevelamer usage than with other phosphate binders [74,76,94–96]. In the CARE study serum bicarbonate levels were significantly lower in the sevelamer group as compared with the calcium acetate group [76]. In a study of 36 patients randomized to placebo or sevelamer, the serum bicarbonate decreased from 22.8 ± 4.6 to 20.9 ± 2.1 mEq/l in the placebo group and from 21.6 ± 4.4 to 20.4 ± 4.1 mEq/l (p = ns) in the sevelamer group over 8 weeks [74]. In a trial of 16 hemodialysis patients, serum bicarbonate levels decreased from 18.2 ± 3.07 to 17.3 ± 3.15 mEq/l after 1 week of treatment (p < 0.05), but then increased to 19.0 ± 2.7 mEq/l after 6 weeks of treatment (p = ns) [94]. Results from most studies seem to indicate that sevelamer has little effect on serum bicarbonate concentration, while other phosphate binders contain alkali and have a beneficial effect on serum bicarbonate concentrations [74,76,94–96]. Metabolic acidosis has been cited as a potential concern because it may promote bone resorption and exacerbate secondary hyperparathyroidism [97,98]. However, these effects have not been seen in clinical trials of sevelamer. In fact, sevelamer treatment is associated with an increase in trabecular bone density [42].

Usage in children

Sevelamer has been studied in children and appears effective [88]. In a 6-month open-label trial of 17 patients aged from 2 to 18 years (mean age 11.8 ± 3.7 years), sevelamer resulted in a decrease in serum phosphorus levels from 7.5 ± 2.2 to 6.2 ± 1.2 mg/dl (p < 0.01). The serum calcium, serum bicarbonate, parathyroid hormone level, total cholesterol and LDL cholesterol did not change significantly during the study. The baseline total serum cholesterol was 176 ± 92 mg/dl and decreased to 153 ± 50 mg/dl at the end of the study. These changes were not significant, which might reflect the small sample size. Patients were taking an average of 163 ± 46 mg/kg/day (6.7 ± 2.4 g/day) at the end

of the study. The medication was well tolerated and there were no adverse events reported. Querfeld has reviewed the current usage of phosphate binders in pediatric patients [99]. As in adults, a pertinent issue with the use of calcium-based binders is the risk of developing cardiovascular calcification [37]. In his review, Querfeld noted a decrease in serum bicarbonate levels in an ongoing trial using sevelamer in children, though values were not included. Clearly, acidemia can delay skeletal growth and would be an important factor to treat or avoid in children.

Drug interactions

Sevelamer does not interfere with the absorption or excretion of digoxin, warfarin, enalapril or metoprolol [100,101]. Sevelamer has no significant effect on the pharmacokinetics of cyclosporin A, but reduces the area under the curve (AUC) and maximum plasma concetration (C_{max}) of mycophenolate mofetil [102]. The oral bioavailability of ciprofloxacin is significantly reduced by sevelamer and by calcium carbonate, suggesting reduction of antimicrobial efficacy and increase in the risk of bacterial resistance [103].

When a patient is concomitantly receiving sevelamer and any oral drug for which blood concentrations determine safety or efficacy, the other drug should be administered 1 h before or 3 h after sevelamer [104].

Conclusions

Sevelamer is a non-absorbed, calcium-free, metal-free phosphate binder. Numerous studies have shown sevelamer effectively reduces serum phosphate levels. Sevelamer is less likely to cause hypercalcemia than calcium-based phosphate binders. Substituting sevelamer for calcium-based phosphate binders dramatically decreases the total calcium load to within NKF guidelines [35,36,40]. Several studies have shown sevelamer attenuates the progression of cardiovascular calcification in chronic hemodialysis patients. Furthermore, numerous studies have shown that serum total and LDL cholesterol decline significantly during treatment with sevelamer. Sevelamer treatment led to a significant increase in trabecular bone density in one study.

Expert commentary & outlook

Historically, calcium-based binders have been used to treat hyperphosphatemia in dialysis patients. Concerns regarding total body calcium overload were noted at the onset of the use of these agents, and then resurfaced more recently with the increased interest in the accelerated cardiovascular death rate of dialysis patients. The development of sevelamer allowed the use of an effective, safe, calcium-free phosphate binder for the first time. Sevelamer was shown to effectively bind phosphate and resulted in a marked decrease in body calcium burden. The Treat-to-Goal study was a pivotal study that showed a markedly decreased progression of vascular calcification in individuals treated with sevelamer compared with individuals treated with calcium-based binders. This was the first study to identify a clinical end point other than changes in serum values of calcium and phosphorus. Over time, the use of sevelamer has increased significantly and the results of the Treat-to-Goal study are likely to lead to further increases in the usage of this agent.

Lanthanum is a new agent that is also calcium free. Long-term studies have all showed safety for this medication which should dispel the concerns of some nephrologists regarding heavy metal deposition in bone and other organs. The price differential between lanthanum and sevelamer, as well as the marketing techniques used for these medications, is likely to be an influential factor in determining the usage patterns of these agents in the future.

Patient tolerability is also likely to be an important factor in determining the usage of these medications. Lanthanum is a large chewable tablet, with a taste similar to Tums® (GlaxoSmithKline). Sevelamer is a caplet that is swallowed. In general, patients taking sevelamer are required to take between two to six caplets with each meal or snack. Patients taking lanthanum will be required to take one to two large, chewable tablets with each meal or snack. Patients need to take these medications with each meal and snack on a daily basis for all the years they are on dialysis. Therefore, differences in patient palatability, even if mild, will affect compliance and affect response to medications and thus prescription over time. Some patients may prefer to take a large number of pills, while others will prefer a chewable preparation.

Another important factor will be the results of the Dialysis Clinical Outcomes Revisited (D-COR) study. The current trial is examining differences in morbidity and mortality outcomes among patients treated with sevelamer versus patients treated with calcium-based phosphate binders. This is the first study that will examine primary outcome data (morbidity and mortality) in individuals based upon phosphate binder

usage. If a decline in morbidity and mortality is identified with the usage of sevelamer, it is likely that the usage of this agent will expand markedly. Initial results from this study are expected in mid-2005.

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Highlights

- Calcium-based phosphate binders were the standard of care for treatment of hyperphosphatemia related to kidney failure.
- The introduction of a noncalcium-based phosphate binder (sevelamer hydrochloride) has allowed for control of serum phosphorus without increases in calcium burden.
- An increased calcium burden has been associated with accelerated cardiovascular calcification in dialysis patients.
- In a randomized trial, sevelamer has been found to significantly slow the progression of cardiovascular calcification compared with calcium-based binders in dialysis patients.
- Lanthanum carbonate, a newer calcium-free phosphate binder has recently been introduced. It appears effective in controlling hyperphosphatemia.
- The Dialysis Clinical Outcomes Revisited (D-COR) study will be the first clinical trial examining the effect of phosphate binders (sevelamer vs. calcium-based agents) on the primary end points of morbidity and mortality.

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