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Review Article

OVERALL EFFECTS OF SEVELAMER IN THE TREATMENT OF HYPERPHOSPHATEMIA: A REVIEW

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ABSTRACT

The term 'Chronic Kidney Disease-Mineral And Bone Disorder' (CKD-MBD), coined in 2006, was introduced in a position statement by the Kidney Disease: Improving Global Outcomes (KDIGO) organization. Serum phosphate is an independent predictor of cardiovascular morbidity and mortality in patients with chronic kidney disease and the general population. There is accumulating evidence that phosphate promotes arterial stiffening through structural vascular alterations such as medial calcification, which are already apparent in the early stages of chronic kidney disease.Phosphate-binder therapy for hyperphosphataemia is key to the treatment of patients with chronic kidney disease (CKD)-mineral and bone disorder (MBD).In particular, it is recommended that the use of calcium-based phosphate binders should be restricted in patients with hypercalcaemia, vascular calcification, low levels of parathyroid hormone (PTH) or adynamic bone disease; as the use of calcium carbonate can favour the progression of vascular calcifications. In the presence of adynamic bone disease, calcium load has a significantly higher impact on aortic calcifications and stiffening There is evidence of reduced progression of vascular calcification in patients treated with Sevelamer compared with high doses of calcium-based binders. Nevertheless, a number of experimental and observational findings seem to suggest that sevelamer should be preferred over calcium-based binders, in as much as these can increase cardiovascular mortality when used in high doses.Sevelamer sequesters phosphate within the gastrointestinal tract, so prevents its absorption and enhances its faecal excretion. This review summarises an overall effect of sevelamer in hyperphosphatemic therapy.

Keywords: sevelamer hydrochloride, sevelamer carbonate, hyperphosphatemia.

INTRODUCTON

Hyperphosphatemia indicates ''A silent killer of patients with renal failure''. Half of patients with levels of serum phosphorous at the upper limit don't survive after 4 years.[1] The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines underlined the negative role of hyperphosphataemia in determining derangement of bone metabolism and of the CV system in CKD patients. The pathophysiology of CKD is complex. Events of underlying disorders of bone and mineral metabolism have an origin early in kidney disease. Mechanisms of calcification are triggered very early with derangement of Na/P transport at the level of vascular smooth muscle cell and sequential calcified vessel.[2] Primary care physicians typically play a key role in the early treatment and management of patients with CKD. The most common point of referral to the nephrologist is usually at stage 4 or even 5, point where most of the above have already been established and evolved from latent to apparent symptoms.[3]

Over the succeeding years, large numbers of patients have been treated with Sevelamer, and it has fulfilled expectations in helping to control the hyperphosphataemia of end-stage renal failure. Additionally treatment with sevelamer was accompanied with

lower incidence of hypercalcemia, decreased incidence of low PTH levels, decrease of LDL-cholesterol both in dialysis and predialysis patients, decreased C-reactive protein, amelioration of hyperuricemia and low fetuin A and decrease of uremic toxins, suggesting an overall anti-inflammatory effect. In incident dialysis patients, treatment with sevelamer has been associated with better survival, while in prevalent patients a clear benefit could only be demonstrated in older patients and in patients treated for more than 2 years. True hyperphosphatemia is usefully subdivided according to (a) whether phosphorus is added to the extracellular fluid from a variety of exogenous or endogenous sources, or (b) whether the urinary excretion of phosphorus is reduced from either decreased glomerular filtration or increased tubular reabsorption. Severe hyperphosphatemia, defined herein as levels of 14 mg/dL or higher, is almost invariably multifactorial--usually resulting from addition of phosphorus to the extracellular fluid together with decreased phosphorus excretion. The hyperphosphatemia of the patient described herein appeared to result from a combination of dietary phosphorus supplementation, acute renal failure, acute pancreatitis, and ischemic bowel disease, complicated by lactic acidosis.

SEVELAMER

In 1997 sevelamer hydrochloride (Renagel®) and in 2007 the newer sevelamer carbonate (Renvela) were presented as nonabsorbable agents that contain neither calcium nor aluminum. These drugs are cationic polymers that bind phosphate through ion exchange, in the gastrointestinal tract. As noted with other phosphate binding agents, a significant number of trials have found that sevelamer is effective in lowering serum phosphate levels[13–18]. The important issues with respect to the choice of sevelamer versus other agents are their relative effects on mortality, vascular calcification, bone disease, and biochemical effects, particularly hypercalcemia. The following sections will address some of the evidence evaluating the relative effects of sevelamer on mortality, vascular calcification, and biochemical indices.[4]

Effect on mortality

A small number of randomized trials and a metaanalysis have evaluated mortality with sevelamer versus calcium-based phosphate binders. The following is a brief review of the largest studies:

The three-year Dialysis Clinical Outcomes Revisited (DCOR) trial evaluated mortality and morbidity outcomes among 2103 prevalent hemodialysis patients randomly assigned to either sevelamer or calcium-based phosphate binders[9]. A secondary analysis reported no differences in mortality, but there were benefits with sevelamer on all cause hospitalizations and hospital days[12]. DCOR is the largest prospective outcomes study ever conducted in dialysis population. This 3-year trial enrolled more than 2100 patients (50% of patients were diabetic) and compared the difference in outcomes for patients receiving sevelamer hydrochloride with those receiving calcium-based phosphate binders in 75 sites in the United States. Patients were randomly assigned to either sevelamer hydrochloride (Renagel®) or calcium-based binders (PhosLo® [calcium acetate] or TUMS® calcium carbonate). The median age of patients in the study was 62 years old. Up to 45 months, there was no significant difference in all-cause mortality (RR 0.93, 95% CI 0.79- 1.11) and cardiovascular mortality (RR 0.93, 95% CI 0.74-1.17) though a 7% reduction in mortality in favor of sevelamer was noticed p=0.40). However, a clinically meaningful benefit was associated with sevelamer use for older patients. In a pre-specified secondary analysis, those 65 years or older achieved a 23% reduction in all-cause mortality compared with those 65 or older using calcium-based phosphate binders, a result that was statistically significant in favor of the sevelamer-treated patients (p=0.02). The mean number of hospitalizations per patient per year was lower in the sevelamer-treated arm (p=0.07), with the biggest difference seen in patients > 65 years. Additionally, for patients remaining on study for at least two

years (43% of the study population) a difference in mortality emerged favoring the sevelamer patients (p=0.02).[5-13]

Effect on calcification

There appears to be relatively less progression of vascular calcification with sevelamer versus calciumcontaining phosphate binders among patients with CKD. The prospective and randomized "Treat-to-Goal" andRenagel in New Dialysis Patients (RIND)trials both reported relatively less progression of coronary artery calcification with sevelamer versus calcium-containing phosphate binders[14]. By comparison, the Calcium Acetate Renagel Evaluation (CARE)-2 trial found similar progression of coronary artery calcification with sevelamer and calcium acetate after intensive lipid control[15]. The differences observed between the "Treat-to-Goal", RIND, and the CARE-2 trial may be due, in part, to study limitations of CARE- 2. Treatment assignment was not blinded in CARE-2, the 1.8 a priori margin for drug equivalence in favor of calcium acetate was large, CAC is only a surrogate outcome, duration of treatment was short(1-year), and dropout rate was high.In incident dialysis patients, treatment with sevelamer has been associated with better survival, while in prevalent patients a clear benefit could only be demonstrated in older patients and in patients treated for more than 2 years. In conclusion, the treatment of hyperphosphatemia with sevelamer hydrochloride, a noncalcium and nonmetal containing phosphate binder, is associated with a beneficial effect on vascular calcification progression, bone disease and most likely with a survival benefit in some hemodialysis patients populations[16].

Given these findings, the risk of long-term calcium exposure remains a concern. Limiting calcium-containing phosphate binder use and the early use of sevelamer in patients with persistent hyperphosphatemia, even in combination with calcium-containing binders, may be most appropriate.

Effect on markers of bone turnover

An 8-week, prospective, open-label, randomized study was conducted after a 2-week washoutperiod in chronic hyperphosphatemic HD patients. This study compared the effect of sevelamer on markers of bone turnover with that of calcium acetate, as stratified by baseline serum intact parathyroid hormone (iPTH) level. There was no difference in the changes of serum phosphorus, calcium-phosphorus product and serum iPTH between the sevelamer and the calcium acetate groups. However, more hypercalcemic events (12%) were documented under calcium acetate treatment. In patients with hypoparathyroidism, calcium acetate treatment decreased serum iPTH at the end of the study, while sevelamer did not. Increased serum alkaline phosphatase levels were found among patients receiving sevelamer treatment compared with those who received calcium acetate treatment. In those patients receiving sevelamer, the serum alkaline phosphatase level was also positively correlated to the sevelamer dosage ($r = 0.246$, $p = 0.013$).Sevelamer effectively reduces serum phosphorus with a lower incidence of hypercalcemiceffects in HD patients. Sevelamer is an effective means of treatment for chronic hyperphosphatemic HD patients, especially those with hypoparathyroidism.[17]

Effect on biochemical parameters

A number of randomized prospective studies have found that sevelamer compared with calcium-based phosphate binders is associated with lower serum calcium levels and higher phosphate and PTH levels[18,]. In the prospective "Treat-to-Goal" trial, 200 patients undergoing maintenance hemodialysis were randomly assigned to sevelamer or calcium-based phosphate binders. At one year, although serum phosphate control was similar with both agents, sevelamer was associated with the following:

- Lower incidence of hypercalcemia (5 versus 16 percent)
- A minimal decrease in the serum calcium concentration (9.5 versus 9.7 mg/dL)
- Decreased incidence of low PTH levels (30 versus 57 percent)

- Sevelamer causes 15-31% decrease of LDL-cholesterol both in dialysis and predialysis patients[19].
- C-reactive protein levels decreased significantly after 52 weeks in sevelamer receiving patients while remained unchanged in calcium binder arm, suggesting an antiatheromatous, anti-inflammatory action of the drug[20].
- Use of sevelamer has been associated with amelioration of hyperuricemia, low fetuin A, decrease of uremic toxins, suggesting an anti-inflammatory action[21].

Although conventional dosing of sevelamer is effective, compliance with the requirement for thrice daily dosing with any phosphate binder can be problematic. A small crossover study found that thrice daily and once daily dosing were equally effective[22]. Although furtherstudy is required, once daily dosing may simplify the dosing regimen, thereby resulting in increased compliance and overall efficacy.

One problem associated with sevelamer hydrochloride is the possible induction of metabolic acidosis. As a result, a buffered form of sevelamer, sevelamer carbonate (Renvela®), has been developed. It is associated with higher serum bicarbonate levels than sevelamer hydrochloride (Renagel®), but these agents appear to be equivalent in their ability to control phosphate levels. This was shown in a double-blind randomized trial of 79 hemodialysis patients in which patients were administered eight weeks of sevelamer carbonate or sevelamer hydrochloride and then crossed-over to the other agent for eight weeks[23]. Both agents similarly controlled mean serum phosphate levels, while bicarbonate levels were significantly higher with sevelamer carbonate (+1.3 mEq/L). Additional advantages of sevelamer carbonate (Renvela®) over sevelamer hydrochloride would be multiple dose forms of sevelamer carbonate, not only in tablet, but also in a powder that will be able to be mixed with a liquid and then have taken as an emulsion, that is, alternative dose forms. Also, the ability to lessen or eliminate acidosis with the carbonate moiety of Renvela ® compared with the hydrochloride in Renagel® is a big benefit. Overall adverse reactions among those treated with sevelamer hydrochloride occurring in > 5% of patients included: vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), flatulence (8%) and constipation (8%). If the clinical trial and cross-over design is held out in larger use, then it looks like the GI side effects won't even be an issue at all with sevelamer carbonate.

And thus it was concluded that Sevelamer treatment resulted in no statistically significant changes in bone turnover or mineralization compared with calcium carbonate, but bone formation rate increased and trabecular architecture improved only with sevelamer. In conclusion, the treatment of hyperphosphatemia with sevelamer hydrochloride, a noncalcium and non-metal containing phosphate binder, is associated with a beneficial effect on vascular calcification progression, bone disease and most likely with a survival benefit in some hemodialysis patients populations.

Effect on endotoxin binding

Endotoxin (ET) is a Gram-negative bacterial cell wall component and a potent stimulus for innate immune system activation leading to the transcription of proinflammatory cytokines (e.g., IL-1, IL-6, and TNFα) that adversely affect protein metabolism and nutrition.Reductions in serum ET concentrations in hemodialysis patients have been observed withsevelamer therapy in observational studies and the few published interventional studies. Reduction of ET concentrations was associated with concomitant reductions in TNFα, IL-6, and CRP and improvement in serum albumin in the majority of these small studies.[24]

The inflammatory stimulus associated with elevated ET concentrations has been linked to increased cardiovascular disease(CVD) risk with End Stage Renal Disease (ESRD) patients and may explain, in part, the markedly increased CVD death rate in hemodialysis patients.[25-28]

Effect on LDL cholesterol level

Sevelamer has been found to bind to bile acids in vitro and *in vivo* probably due to its physiochemical similarities to common bile sequestrants, thereby interfering with fat absorption and reducing low-density lipoprotein (LDL) cholesterol levels. The use of calcium carbonate can favour the progression of vascular calcifications. There is evidence of reduced progression of vascular calcification in patients treated with sevelamer compared with high doses of calcium-based binders, but there is as yet no strong evidence regarding hard outcomes, such as mortality or hospitalization, to support the use of one treatment over another. Nevertheless, a number of experimental and observational findings seem to suggest that sevelamer should be preferred over calcium-based binders, in as much as these can increase cardiovascular mortality when used in high doses.[29]

Effect on cardiovascular structure and function in chronic renal impairment

A single-centre prospective, randomised, double-blind, placebo-controlled trial of 120 subjects with stage 3 CKD (defined as an estimated GFR 30-59 ml/min/1.73 m^2) established on conventional treatment with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker for at least 3 months before enrolment. GFR was estimated by the 4-variable Modification of Diet in Renal Disease formula with serum creatinine recalibrated to be traceable to an isotope derived mass spectroscopy method. The demonstration of an important pathophysiological role for serum phosphate in the development of cardiovascular disease associated with CKD would be crucial in the understanding of this condition and have important implications for treatment. As left ventricular mass and arterial stiffness are prognostically significant markers in CKD, a positive effect would suggest that phosphate lowering in stage 3 CKD with the non-calcium-based phosphate binder sevelamer, in addition to conventional treatment for blood pressure and hypercholesterolaemia, is of prognostic value and would provide a rationale for a large clinical trial with cardiovascular morbidity and mortality as end-points.Phosphate binding with sevelamer carbonate reduced left ventricular mass, improved indices of left ventricular systolic and diastolic function, and reduced arterial and cardiac stiffness in patients with stage 3 CKD.[30]

Effect on serum inflammatory profile, soluble CD14, and endotoxin levels in hemodialysis patients

A prospective, randomized, open-label, parallel design trial was conducted in fifty-nine stable hemodialysis (HD) patients, 30 receiving sevelamer, and 29 receiving calcium acetate were evaluated. Serum levels of inflammatory parameters (high-sensitivity C-reactive protein [hs-CRP], TNF-α, interleukin (IL)-1, -6, -10, and -18), as well as endotoxin and sCD14 concentrations, were measured at baseline and after 3 months of therapy. It was found that administration of the noncalcium phosphate binder sevelamer to maintenance HD patients is associated with a significant decrease in hs-CRP, IL-6, serum endotoxin levels and sCD14 concentrations.[31,32]

Comparison of efficacy of the phosphate binders nicotinic acid and sevelamer hydrochloride in hemodialysis patients.

Studies comparing the effects of sevelamer and nicotinic acid, both similar non-calcium and non-aluminum phosphate binders, that although nicotinic acid reduced hyperphosphatemia,sevelamer showed higher efficacy in controlling hyperphosphatemia as well as the Ca-P product.[33]In this study, 40 patients on HD with a serum phosphorus level of more than 6 mg/dL were enrolled. After a two week washout period without phosphate binders, the patients were randomly divided into two equal groups (n=20) and were started on nicotinic acid or sevelamerfor a period of four weeks. The dose of nicotinic acid used was 500 mg and that of sevelamer was 1600 mg daily. Blood samples were drawn for the measurement of the total calcium (Ca), phosphorus (P), alkaline phosphatase

(ALP), triglyceride (TG), total cholesterol (Chol), high-density lipoprotein (HDL), low-density lipoprotein (LDL), uric acid and parathyroid hormone (PTH). Patients receivingsevelamer showed a significant reduction in serum P level (2.2 ± 0.69 mg/dL; P <0.0001) in comparison with the nicotinic acid group (1.7 ± 1.06 mg/dL; P = 0.004). Reduction in the Ca-P product was significantly different in the two groups; in the sevelamer group, it was 21 ± 7; (P <0.0001) while in the nicotinic acid group, it was 16 ± 11 (P = 0.007). Also, patients on sevelamer showed greater reduction in the mean TG level (38.9 ± 92 mg/dL; P = 0.005).

Comparison of efficacy, safety & other clinical effects of the non-calcium phosphate binders

Randomised controlled studies consistently show that sevelamer and lanthanum carbonate offer equivalent lowering of serum phosphorus and often effectively achieve phosphorus targets versus calcium salts, with sevelamer having a positive effect on bone disease, vascular calcification, and patient-level outcomes in dialysis patients in several trials. There is also evidence that lanthanum carbonate can improve bone health, but data are limited to its effects to vascular calcification or patient-level outcomes. Magnesium salts have also been shown to reduce serum phosphorus levels, but clear evidence is lacking on bone, vascular, or clinical outcomes. It also remains to be established whether long-term systemic accumulation of lanthanum and magnesium, in tissues including bone, has clinically relevant toxic effects. This review summarises the evidence of efficacy and safety for newer calcium-free phosphate binders in CKD-MBD management.[33]

Effect of sevelamer and calcium acetate in children with CKD

A multicenter, randomized, open-label, crossover study was performed to compare the efficacy and safety of sevelamer, a calcium-free phosphate binder, with calcium acetate in pediatric patients (age, 0.9 to 18 years) with chronic kidney disease (CKD). 2 weeks of washout followed by 8 weeks of treatment with either sevelamer or calcium acetate in a crossover fashion. Phosphorus, calcium, and intact parathyroid hormone in serum were measured every 2 weeks, and phosphate binder dosages were adjusted, if needed. Serum lipid and vitamin concentrations were measured at the beginning and end of each treatment period. The primary end point was the decrease in serum phosphorus levels after 8 weeks of treatment.Treatment of children with CKD with sevelamer and calcium acetate provides similar phosphorus level control. The marked decrease in lipid levels and lower rate of hypercalcemia may augment the long-term benefit of sevelamer.[34]

Effect of sevelamer carbonate andlanthanum carbonate on the pharmacokineticsof oral calcitriol

The study investigated whether concomitant SC or LC affected the pharmacokinetics of oral calcitriol in healthy volunteers. In this openlabel study, 41 volunteers were randomized to 1 of 6 treatment sequences with each sequence consisting of 3 treatment periods: Calcitriol only (2 . 0.5 μg at lunch); calcitriol + LC (1 . 1000 mg at breakfast, lunch and dinner); calcitriol + SC (3 . 800 mg at breakfast, lunch and dinner). Treatment periods were separated by a 7-day washout and meals were standardized. Serum calcitriol concentrations were assessed by radioimmunoassay at baseline for each study period and at various time points post-dosing (up to 48 h). Exogenous calcitriol levels were calculated as total serum calcitriol minus baseline endogenous levels in each study period. Area under the curve over 48 h (AUC0–48) and maximum exogenous calcitriol concentration (Cmax) were analyzed using a mixed effect linear model with baseline endogenous calcitriol as a covariate. Mean age of the participants was30 ± 7.6 years and 54% were men. There were no significant changes in least square mean AUC0–48 or Cmax calcitriol values when LC was co administered with calcitriol (AUC0–48, calcitriol + LC vs. calcitriol alone: 429 vs. 318 pg.h/ml, p = 0.171; Cmax: 47.0 vs. 49.7 pg/ml, respectively, p = 0.313). In contrast, co-

administration of SC with calcitriol resulted in a significant reduction in least square mean AUC0– 48 for calcitriol concentration compared with calcitriol alone (calcitriol + SC: 137 pg.h/ml vs. calcitriol alone: 318 pg.h/ml; $p = 0.024$). Coadministration with SC was associated with a reduction in least square mean Cmax for calcitriol (calcitriol + SC: 40.1 pg/ml vs. calcitriol alone: 49.7 pg/ml; $p < 0.001$). The data shows that SC reduces the bioavailability of oral calcitriol by about 57%; LC has no significant or clinically relevant effect. This may be an important consideration in patients with CKD who often use oral vitamin D supplementation.[35]

Sevelamer in early stages Nondialysis-Dependent Chronic Kidney Disease (NDD-CKD) dominates calcium carbonate through reduction of deaths and hospitalizations

The independent study showed for the first time a significant reduction in mortality associated with Sevelamer, a phosphate binder, compared to Calcium Carbonate, in stage 3-4 nondialysis-dependent CKD patients. The study evaluated the impact on CKD related hospitalizations in order to assess the cost-effectiveness profile from the NHS perspective. The independent study involved 107 (Sev) and 105 (CaC) patients with a 36 months follow-up. Individual hospitalizations in Nephrology, Cardiology and ICU were recorded as well the overall length of stay over the observation period. Correlated consumption of drugs, such as alpha and beta blockers, ARBs, ACE inhibitors, calcium channels blockers and erythropoietin, was also assessed. For hospitalizations and drugs, DGR tariffs and hospital acquisition cost respectively were used. As effectiveness end-point we considered the number of averted deaths. The result was that Calcium-treated patients were associated with greater frequencies of admission in all departments, thus generating significantly higher costs. The average savings generated by reduced hospitalizations far exceeded the acquisition cost of Sevelamer. In case of hospitalization, Sevelamer-treated patients showed a substantial reduction in the overall length of stay (-5.9 days, p_0.012). Such difference was also present in the secondary subgroup (-5.5 days, p_0.13). After 1000 bootstrap sampling, the primary analysis provided a mean cost difference of -€2282_/_€27 (CI 95%) and mean effectiveness difference of 0.09_/_ 0.006 averted deaths in favor of Sevelamer. Similar figures were present in the secondary subgroup analysis (-€2403 _/_ €28 and 0.15 _/_ 0.007). Sevelamer showed a dominance profile in 84% and 90% of all simulations. Thus it was concluded that early use of Sevelamer in NDD-CKD patients proved more effective and less costly, generating good value for money from the NHS perspective.[36]

Health and economic consequences of sevelamer use in hyperphosphatemia

The safety and efficacy of Renagel® (sevelamerhydrochloride) in binding phosphate in patientswith end stage renal disease and its ability to attenuatethe progression of cardiac calcification has been well documentedbut not the longer-term health and economicconsequences. Thus, a model of the predicted longtermconsequences of Renagel® compared to calciumbasedbinders (acetate and carbonate) was developed.Along-term cardiovascular implications ofone year of treatment with phosphate binders in patientson hemodialysis are estimated based on the patient's demographics, co morbidities, and physiologic and renalparameters. The initial calcification score and expectedchanges over one year are derived using regression equationsdeveloped from the Treat-to-Goal study and translatedto cardiovascular disease risk based on equationsdeveloped from a long-term cohort study (London). Theimplications of cardiovascular disease for life expectancyand medical costs are accounted for from a US payer perspective.In a population of 100 patients, thecardio-protective effect of Renagel® over 1 year is estimatedto prevent 9 future cardiovascular events and tosave 18 life years compared with calcium acetate; and 10events and 18 life years compared to carbonate. Theseevents would cost $205,600 and $226,700 to manage.These

benefits are obtained at a net cost of about $37,900and $19,500, respectively. The incremental costeffectivenessratios amount to $2200 and $1100 per(discounted) life year gained; and $4400 and $2300 percardiovascular event prevented. It was concluded thatwidespreaduse of Renagel® for treatment of hyperphosphatemiain patients on hemodialysis may seem like justanother burden on already strained health care resources.In the context of dialysis, at a median cost-effectivenessratio of $46,000 per life year gained, the results of thisstudy provide evidence that such intervention would beeconomically sound.[37]

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