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Hyperphosphatemia in Chronic Kidney Disease: Drug Treatment and Effects on Metabolic Acidosis. A Mini Review

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Abstract

Hyperphosphatemia is a highly prevalent component of CKD and chronic kidney disease mineral bone disease (CKD-MBD). Its association with metabolic acidosis, hypertension, cardiovascular disease and chronic inflammation is common. Treatment is commonly with calcium based phosphate binder (PB) as the high cost of sevelamer makes it readily unavailable particularly in low income settings. Sevelamer has several comparative advantage over calcium based PBs, many of which, in addition to its non-worsening of tissue calcification contributes significantly to positive treatment outcome. The ability of sevelamer to reduce many cytokines and inflammatory mediators such as TNF-α, IL-1, IL-6, FGF-23 and high sensitivity CRP among others, contributes significantly to its renoprotection prowess.

A concerted effort at increasing its availability particularly in low income settings is needed to maximize its beneficial role in CKD management.

Keywords: Hyperphosphatemia; Sevelamer; Calcium based phosphate binders; Metabolic acidosis; Inflammation; Chronic kidney disease; Cardiovascular disease

Introduction

Chronic kidney disease had remained a major health burden for victims of the disease and their care givers, and this burden is occasioned by several associated comorbid conditions like metabolic acidosis (MA) and cardiovascular dysfunction leading to higher morbidity and mortality rates [1,2]. The accumulation of volatile acids in the blood stream (which defines MA) is progressively associated with lower serum bicarbonate concentration (SBC), low blood PH, fluid accumulation in the interstitial spaces, hyperparathyroidism, hypersphosphatemia (and in most cases hypocalcemia), anemia and chronic kidney disease mineral bone disease (CKD-MBD) [3-8]. Hyperphosphatemia mediates renal osteodystrophy, metastatic calcification and increased morbidity and morbidity [3,5,7].

Acid accumulation in CKD is primarily secondary to a decline in renal excretion of exogenous acids, associated increased acid load, release of inflammatory cytokines and oxidative stress. MA can initiate and accelerate CKD-MBD [8,9]. Hyperparathyroidism in CKD is commonly of the secondary type, with hypocalcemia, hyperphophatemia and reduced bone mineralization. Calcium is therefore mobilized from the bone to buffer the acidosis and increase SBC and blood PH [7-10]. Hyperphosphatemia as a component part of CKD-MBD mediates endothelial damage (with atherosclerosis), cardiovascular dysfunction, inflammation with cytokine release and oxidative stress [4,6-8]. The interplay of these forces, with their outcome, determines the negative impact of hyperphosphatemia [11]. The management of hyperphosphatemia in CKD is usually all-encompassing, with normalization of serum levels of calcium, phosphate, Vitamin D and parathyroid hormone (PTH) as targets [12-14].

Phosphate binders could be calcium based or non-calcium based. The adverse effects of Sevelamer hydrochloride (HCL) and Calcium carbonate on gastrointestinal tract function underlies their phosphate and/or oxalate chelating effects. While sevelamer HCL induces anti-inflammatory features, its exchanges of a bicarbonate ion with a chloride ion generates a H+ ion [15] Likewise, calcium being a base, buffers acids.

Sevelamer Hydrochloride and Metabolic Acidosis in Chronic Kidney Disease

Sevelamer is a high molecular weight, rather expensive, non-absorbable, calcium-free and Aluminum-free exchange resin that binds phosphate in the gastrointestinal tract (GIT) thereby preventing its absorption and enhancing its GIT elimination [1-4]. The SBC starts decreasing as CKD progresses through the stages. Some drugs used in managing CKD can impact the MA with sevelamer HCL reported to aggravate it, sevelamer carbonate and calcium carbonate partially ameloriates it while Bixalomer, from Japan was reported to improve it [16]. Worsening of the CKD-induced hypobicarbonatemia results from the 1:1 exchange (buffering) between bicarbonate and chloride ions. The replacement of the HCL in the sevelamer molecule with carbonate (CO_3) prevented the HCL-precipitated MA by abolishing the exchange between HCO_3 and chloride and secondly, by the generation of the HCO_3 ion from the metabolism of the CO_3, a process also seen with calcium carbonate [17-20]. Metabolic acidosis aggravates the symptomatology of CKD, worsens morbidity and mortality and could increase the risk of hospitalization [21,22]. The interplay between MA and inflammatory injuries involves all organ/systems of the body, relating to the initiation, progressions and manifestations of these changes typifies the symptom complex of CKD [23].

Chronic inflammation has long been known to be a co-factor, initiator and facilitator of kidney damage. Treatment regimen for CKD have therefore been formulated with the aim of preventing, minimizing or removing this [23-26]. A major part of sevelamer's renal protection profile could be its anti-inflammatory ability. It's pleitropic features have been reported to involve chelating phosphate ions and other pro-inflammatory mediators, and cytokines including TNF-α, IL-6 and 8-isoprostanes and also, its lipid lowering features which further buttress its positive impact on cardiovascular function, structure and outcome [27-30]. The fact that sevelamer limits cardiac calcification, unlike the calcium based phosphate binders may be mostly related to its calcium and lipid lowering ability, and been able to limit the inflammatory changes that precedes and accompany cardiac and vascular remodeling and calcification [31-34].

Phosphate Binders and Cardiovascular Function in Chronic Kidney Disease

The positive impact of sevelamer on cardiovascular function was reported by authors that found lower values of fibroblast growth factor 23 (FGF-23) and Klotho with sevelamer use [35-39]. FGF-23 is a hormone produced by the osteocytes and osteoblasts and mediates phosphaturia while inhibiting calcitriol production [36]. The downregulation of proximal tubule NPT2a is a needed function of the FGF-23 to activate phosphaturia [37-42]. The use of VDRAs such as calcitriol can cause elevation in serum FGF-23. This is secondary to the negative feedback mechanism in mineral and bone metabolism that involves the interplay between serum levels of calcium and phosphate under PTH regulation [43,44]. Elevated FGF-23 is associated with hypertension, chronic kidney disease, cardiovascular disease and its value increases along the stages of CKD [45]. The elevation of FGF-23 with worsening renal disease is in its bit to maintain phosphate excretion and balance [44-48]. Recently, FGF-23 has been implicated in the initiation and propagation of both CKD and cardiovascular diseases Negishi et al. [49] and other authors associated these compounds with cardiovascular dysfunction, left ventricular hypertrophy (LVH) and death [50-52]. This role coupled with its ant-inflammatory, calcium-lowering characteristics gives sevelamer a protective role in cardiovascular function [38,42,47]. Findings by Brandenburg et al. [53] however did not agree with the negative relationship between sevelamer and declining values of FGF-23 and klotho. The calcium-phosphate product, a marker of higher risk of adverse cardiac outcome is also decreased with sevelamer [54].

Studies on the adverse effects of elevated FGF-23 on cardiovascular function revealed a positive relationship between FGF-23 and the plasma volume and this has been identified as the cause of the higher rates of hypertension than in the general population [55]. The higher tendency for atherosclerosis in individuals with elevated FGF-23 also partly explains the higher rates of cardiovascular events and mortality seen with higher FGF-23 levels. It therefore goes to say that the positive cardiovascular profile and outcome seen in patients on sevelamer could be a primary consequence of its FGF-23 lowering ability [44-46]. Similar findings revealing the anti-inflammatory feature of sevelamer are seen from several studies that found it useful in reducing high sensitivity C-reactive protein (hs-CRP), calcium-proctive IL-6 and soluble CD14. Navarro-Gonzalez et al. [56] also found higher serum levels of the anti-inflammatory fetuin-A with sevelamer use.

Sevelamer Pleiotropic Properties

Ikee et al. [57], in reporting the pleitropic qualities of sevelamer, described its roles in bone structure, increases in fetuin-A (anti-inflammatory), limiting anemia and oxidative stress, cardiac events and mortality, and metabolism of trace elements in CKD. In the RIND study, a Randomized Controlled Trial (RCT), Block et al. [58] using an electron-beam CT found an 11-fold increase tissue calcification using calcium-based P04 binders in 129 incident hemodialysis patients. In the RIND extension study, a follow up on the RIND study participants, higher mortality in the calcium group was found, P=0.01 [59].

The tendency of the calcium based phosphate binders to cause more tissue calcification is also reported in several studies. The CARE-2 Study, with a prevalent hemodialysis population of 203, found no difference in tissue calcification between the calcium based and the sevelamer HCL groups [60].

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Likewise, the DCOR study found higher all-cause hospitalization in the calcium group compared with the sevelamer HCL group. The authors however reported that only the elderly that received calcium-based binders had higher mortality rate compared to those that received sevelamer HCL [61] Suki et al. [62] and Chewtor et al. [63] in separate studies found no difference between the two groups regarding all-cause hospitalization.

Anemia is known to negatively impact CKD, more so, with concurrent ongoing chronic inflammatory changes. Anemia with hyperphosphatemia and MA is a tripartite that significantly impacts negative synergistic effects on kidney function. Anemia worsens cardiomegaly and could precipitate heart failure [33]. The irony however is the fact that numerically speaking, decreasing hematocrit values tend to be better tolerated as CKD progresses down the stages. This probably justifies the recommendation by KDOQI that the SBC of patients on maintenance hemodialysis (MHD) should not be less than 22mmol/L, and by KDOQI and several national and regional nephrology-based bodies that hematocrit in the dialysis population is best kept in the 33-36% range whereas higher values are often encouraged in early CKD down to the immediate pre dialysis levels [64-71]. The benefits of sevelamer is further buttressed by findings from studies associating sevelamer with increased responsiveness to erythropoiesis stimulating agents (ESAs), reducing pro-inflammatory cytokines that inhibit erythropoiesis, and reducing resistance to ESAs. The outcome of this complex interplay is increased erythropoiesis, however other authors reported a negative relationship between sevelamer use and serum folic acid (FA) levels and this was associated with a worsening anemia. Schiff et al. [72] also found lower serum folic acid levels and a higher requirement for erythropoietin dose from 52 ± 9 to 68 ± 15IU/kg.

Inflammation involving the renal bed whether in acute or chronic setting is commonly associated with proteinuria. It therefore implies that the anti-inflammatory actions of sevelamer could contribute to renal recovery from acute and chronic inflammatory injuries and damages. In a study involving 31 hemodialysis patients, a significant reduction in invitro reactive oxygen species production in 12 months of treatment with sevelamer, was found [73].

The benefits of using VDRA in managing CKD-MBD is better with sevelamer than with calcium based binders as sevelamer's calcium lowering tends to be compensated for by the increased calcium absorption, unlike in calcium-based binders in which hypercalcemia could easily result from the use of the VDRA and calcium-containing compounds, thereby accelerating tissue calcification and increasing the risk for atherosclerosis, LVH and the occurrence of cardiac failure from systolic and diastolic dysfunction [74].

The Ideal Phosphate Binder in Chronic Kidney Disease

The occurrence and frequency of adverse responses secondary to drugs have always be a major determining factor in the acceptability of the drug. An ideal phosphate binder should have the advantage of being efficacious, cheap, readily affordable and, with minimal side effects. Both the calcium-based phosphate binders and sevelamer are reported to be associated with abdominal discomfort, constipation and at times bloating [75]. Sevelamer, particularly with the HCL moiety, can worsen the acidosis of CKD and worsen the hypocalcemia of CKD, particularly without VDRAs, while calcium-based binders can cause cardiac and vascular remodeling, a risk factor for cardiac event and failure. The introduction of Lanthanium chloride tended to eliminate the challenges associated with earlier phosphate binders as adverse effects such as GIT upsets, acidosis and tissue calcifications found with earlier phosphate binders were very minimal or non-existed [76]. However, the financial burden and the poor availability of Lanthanium chloride has been major limiters in its use.

Conclusion

Hyperphophatemia seen in CKD as with the primary disease (CKD) has remained a major burden on CKD victims and caregivers. Hyperphosphatemia in CKD commonly co-exist with some other CKD comorbidities like metabolic acidosis, CKD-BMD, cardiovascular disease, hypertension, and atherosclerosis which collectively worsen the cardiovascular outcome. The significant role played by chronic inflammation associated with these comorbid conditions on the kidney further accelerate kidney damage leading to higher mortality. Sevelamer have mostly be shown in several studies to mitigate the renal damage seen in hyperphosphatemia by reducing inflammatory cytokines and markers of kidney damage like FGF-23, TNF-α, IL-6, endotoxin, IL-1, high sensitivity C-reactive protein (hs-CRP), calcium-proctive IL-6 and soluble CD14. This better renal-protective role of sevelamer over calcium-based binders is attributable to its calcium-lowering and anti-calcification features. The higher cost of sevelamer makes its availability in low-income settings rather low. National, multinational funding agencies and philantropists would therefore be helpful in making this important drug much more available to the CKD population particularly in low income settings.

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