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PHOSPHATE BINDERS IN CHRONIC KIDNEY DISEASE PATIENTS UNDERGOING HEMODIALYSIS– A REVIEW

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ABSTRACT:

Phosphorus plays a crucial role in various physiological functions, including skeletal development, mineral metabolism, cell membrane phospholipid function, mitochondrial metabolism, cell signalling, and platelet aggregation. The typical daily diet introduces about 1000–1400 mg of phosphorus. Two-thirds of this phosphorus is excreted in urine, while the remaining third is eliminated in stools. Kidney function significantly influences phosphorus excretion, making chronic renal failure the primary cause of hyperphosphatemia. Despite advancements, challenges persist in achieving and maintaining target phosphate levels, particularly in the context of modern diets rich in phosphate additives. A significant percentage of dialysis patients struggle to keep their phosphate levels within recommended ranges, emphasizing the need for ongoing innovations in phosphate management therapies.

KEY WORDS: Phosphate binders, Hyperphosphatemia, Chronic Kidney Disease.

I. INTRODUCTION:

Phosphorus plays a crucial role in various physiological functions, including skeletal development, mineral metabolism, cell membrane phospholipid function, mitochondrial metabolism, cell signalling, and platelet aggregation. In the adult body, approximately 700 g of phosphorus is stored, with 85% in bones, 14% intracellular, and only 1% extracellular. Of extracellular phosphorus, 70% is organic within phospholipids, and 30% is inorganic, with 15% protein-bound and the remaining 85% circulating as free mono- or di-hydrogen forms or complexed with calcium, sodium, or magnesium. Only this latter 15% is freely circulated and measured.[1]

The typical daily diet introduces about 1000–1400 mg of phosphorus. Two-thirds of this phosphorus is excreted in urine, while the remaining third is eliminated in stools. Kidney function significantly influences phosphorus excretion, making chronic renal failure the primary cause of hyperphosphatemia. Phosphate retention initiates early in renal failure due to reduced filtered phosphate load, becoming more pronounced in later stages. [1]

Hyperphosphatemia is a major concern in chronic kidney disease patients in which the serum phosphorus level is elevated. People with Chronic Kidney Disease are at risk of developing cardiovascular disease and this in turn is the leading cause of death among people with chronic kidney disease. Hyperphosphatemia is present in the majority of dialysis patients and is associated with increased risk of cardiovascular mortality. [2]

Phosphate binders are the mainstay of hyperphosphatemia management in End Stage Renal Disease patients on maintenance haemodialysis. They help to prevent the progression of mineral bone disorders by reduction of elevated phosphorous levels. [3]

The paracellular pathway, predominant with Western diets high in phosphorus, is the primary mechanism of intestinal phosphate absorption. [4] Elevated serum phosphorus levels are linked to cardiovascular issues, but concentrations exceeding 5.5 mg/dL persist despite efforts like dietary restrictions, dialysis, and phosphate binders. Novel approaches, such as phosphate absorption inhibitors targeting the paracellular pathway, may offer improved phosphate control.[5]

II. EVOLUTION OF PHOSPHATE MANAGEMENT THERAPIES:

The first phosphate binders are Aluminium Salts which were introduced in the year 1970. They reduce phosphate availability by forming coordination compounds with phosphate ions, creating insoluble aluminium phosphate precipitates in the GI tract. [6]

Calcium-based phosphate binders, introduced in the mid-1980s as a potential replacement for aluminium-based binders, were initially effective, inexpensive, and widely used. [30] However, they were soon recognized for their potential contribution to vascular calcification and increased cardiovascular mortality due to the elevated calcium load associated with their use. Recognizing these adverse effects, guidelines were revised in 2017 to recommend restricting the dose of calcium-based phosphate binders in adults with CKD stages G3A to G5D. [7]

In the 1980s, a combination of magnesium hydroxide and aluminium hydroxide proved effective for phosphate control without causing uncontrolled hypermagnesemia. [29] Calcium acetate/magnesium carbonate was also found to effectively lower phosphorus levels, with a study on dialysis patients showing reduced serum phosphorus without an increased risk of hypercalcemia. [8]

Sevelamer hydrochloride, approved in 2000, offered an advancement by decreasing phosphorus concentrations without increasing calcium load. A Cochrane systematic review found that, in patients on dialysis, sevelamer may lead to lower all-cause death and induce less hypercalcemia compared to calcium-based binders. [28] Despite these benefits, sevelamer hydrochloride was found to worsen metabolic acidosis, leading to the development of sevelamer carbonate as an alternative. [9]

Lanthanum carbonate, approved in 2004, reduces phosphorus levels without increasing calcium load, potentially decreasing the risk of treatment-related hypercalcemia. [31] However, precautions are necessary due to reported serious gastrointestinal events. Accumulation of lanthanum carbonate in the liver has been observed in animal models, but conclusive evidence of hepatotoxicity related to lanthanum is lacking. [10]

Non-calcium, iron-based binders like sucroferric oxyhydroxide (approved in 2013) and ferric citrate (approved in 2014) offer alternatives. Sucroferric oxyhydroxide effectively reduces phosphorus levels with a lower pill burden than sevelamer carbonate. [27] Ferric citrate, while effective in lowering phosphorus, causes significantly higher gastrointestinal side effects according to a meta-analysis. Overall, these phosphate binders provide diverse options for managing hyperphosphatemia in patients with chronic kidney disease. [11]

III. ORAL-PHOSPHATE BINDING DRUGS:

Phosphate is increasingly recognized as a potential causal risk factor for chronic kidney disease (CKD) progression, observed in both experimental models and studies with CKD patients. Proteinuria, a risk for kidney failure, is adversely affected by high phosphate levels, particularly undermining the protective effect of renin-angiotensin system inhibitors. General population observations, regardless of CKD evidence, associate higher serum phosphate levels with albuminuria. [12]

In managing serum phosphorus for kidney patients, goals are based on observational evidence, emphasizing simultaneous control of phosphorus and calcium levels to enhance life expectancy. [32]

Lowering intestinal phosphate absorption through a low-phosphate diet is a crucial first step. Recent findings suggest dietary reduction may be more effective than relying solely on pharmacological interventions. [13]

For haemodialysis (HD) patients, efficient removal of phosphate during dialysis is essential. Additionally, the use of foods or medications that bind with phosphorus, such as antacids or phosphate binders, is recommended. [26] The choice of phosphate binders becomes critical, considering historical issues with aluminium-containing agents. Calcium-based salts, while widely used, can lead to complications such as vascular calcification. [14]

Sevelamer hydrochloride, a non-absorbable phosphate binder, shows promise in reducing phosphate levels without systemic accumulation. [33] It has been associated with delayed progression of coronary artery and aortic calcification, improved survival, and positive effects on inflammatory biomarkers. Lanthanum carbonate, another non-calcium-based binder, effectively controls hyperphosphatemia in short-term trials and is well-tolerated. [15]

Lanthanum carbonate, a non-calcium-based phosphate binder, containing the rare earth element lanthanum, has proven effective and well-tolerated in patients with chronic kidney disease (CKD). [34] Clinical trials have demonstrated its usefulness for short- or long-term treatment, showing dose-related reductions in serum phosphorus levels. [16]

A systematic review and meta-analysis of 960 patients in seven placebo-controlled trials confirmed that lanthanum is well-tolerated and effectively controls hyperphosphatemia during short-term trials. [31] This is consistent with a previous meta-analysis comparing non-calcium phosphate binders to calcium-based agents, where lanthanum significantly reduced end-of-treatment serum calcium and calcium-phosphorus product levels, with similar end-of-treatment phosphorus levels. [16]

Despite observed trends, studies have not found statistically significant differences in cardiovascular mortality and coronary artery calcification between patients receiving calcium-based phosphate binders and those receiving non-calcium-based binders. [17]

The potential explanation for the mortality decreases associated with non-calcium-based binders may be related to slowing vascular calcification. This hypothesis gains support from evidence suggesting that switching from calcium carbonate to lanthanum carbonate as a phosphate binder delayed the progression of calcium calcification in patients on haemodialysis. [18]

OVERVIEW OF AVAILABLE PHOSPHATE BINDERS

DRUG	INITIAL US APPROVAL	MECHANISM
Calcium acetate (PHOSLO)	1990	Combines with dietary phosphate to form an insoluble calcium phosphate complex, which is excreted in faces, resulting in decreased serum phosphate concentration
Sevelamer carbonate (RENVELA)	2000	By binding phosphate in the GI tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in serum
Lanthanum carbonate (FOSRENOL)	2004	Reduces absorption of phosphate by forming insoluble lanthanum phosphate complexes that pass through the GI tract unabsorbed Reduces both serum phosphate and calcium phosphate product by reducing dietary phosphate absorption
Sucroferric oxyhydroxide (VELPHORO)	2013	In the GI tract, phosphate binding takes place by ligand exchange between hydroxyl groups and/or water in sucroferric oxyhydroxide and phosphate in the diet. The bound phosphate is eliminated with feces.
Ferric citrate (AURYXIA)	2014	Ferric iron binds dietary phosphate in the GI tract and precipitates as ferric phosphate. This compound is insoluble and is excreted in the stool By binding phosphate in the GI tract and decreasing absorption, ferric citrate lowers the phosphate concentration in the serum.

Recent meta-analyses comparing non-calcium-based binders to calcium-based ones indicate a reduction in all-cause mortality and vascular calcification with the former. [25] Lanthanum, specifically, demonstrates positive outcomes in serum PTH, calcium-phosphorus product, and cardiovascular markers compared to calcium-based binders. These findings underscore the importance of tailored phosphate binder selection in managing CKD patients, with potential benefits in slowing vascular calcification and improving overall outcomes. [19]

The association with aluminium toxicity, particularly in dialysis patients, leading to bone disease and encephalopathy. [24] Subsequently, calcium-based phosphate binders became the standard choice. These binders, predominantly calcium carbonate and calcium acetate, reduce phosphate absorption by forming insoluble complexes in the gastrointestinal tract. [20]

However, concerns emerged over calcium-based binders contributing to vascular calcification and other complications in patients on haemodialysis. To address this, non-calcium-based phosphate binders like sevelamer hydrochloride and lanthanum carbonate were developed. [23] Sevelamer acts by binding phosphate without adding calcium, proving effective in delaying vascular calcification and offering cardiovascular benefits. [35] Lanthanum, a rare earth element, presents an alternative non-calcium option, showing efficacy in controlling hyperphosphatemia. [22]

Despite advancements, challenges persist in achieving and maintaining target phosphate levels, particularly in the context of modern diets rich in phosphate additives. A significant percentage of dialysis patients struggle to keep their phosphate levels within recommended ranges, emphasizing the need for ongoing innovations in phosphate management therapies. [20]

IV. CONCLUSION:

Hyperphosphatemia develops in most patients with ESRD. It has been addressed as a factor playing an important role in the increased cardiovascular morbidity of these patients, which remains the major cause of death in ESRD and dialysis patients. Treatment with phosphate binders to decrease phosphorous level is therefore required.

Treatment with phosphate binders has achieved this need. The traditional aluminium- and calcium-based phosphate binders have been used, and calcium-based phosphate binders in particular are still currently used, but treatment with these compounds is not free from complications such as aluminium retention and/ or hypercalcaemia. The efforts to search for a non- aluminium and non-calcium phosphate binder has led to the introduction of two compounds, sevelamer hydrochloride and lanthanum carbonate, which, together with other recently developed compounds, the trivalent iron preparations, represent without doubt a step forward in the management and treatment of hyperphosphatemia.

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