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Research Article

EVOLUTION OF PHOSPHATE BINDERS IN CKD PATIENTS ON HEMODIALYSIS

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ABSTRACT

Chronic kidney disease (CKD) patients on hemodialysis often struggle with hyperphosphatemia, a condition that significantly increases cardiovascular disease risk and mortality. Phosphate binders, taken orally with dietary phosphate restrictions, are key in managing elevated serum phosphate levels. Traditional binders include calcium-based and aluminum-based options, while newer alternatives are non-calcium-based binders such as sevelamer, lanthanum, and iron-based agents like ferric citrate.

Calcium-based binders, like calcium carbonate and calcium acetate, are widely used due to their cost-effectiveness, despite potential gastrointestinal side effects and the risk of hypercalcemia. Sevelamer, available as hydrochloride and carbonate, avoids calcium-related issues and has shown benefits in reducing serum phosphorus and improving lipid profiles. Ferric citrate, an iron-based binder, offers dual benefits of lowering phosphate levels and improving iron stores, thus aiding in anemia management.

Despite advancements, challenges remain, including medication adherence and potential long-term safety concerns with iron-based binders. Future research is essential to address these challenges and optimize phosphate management in CKD patients.

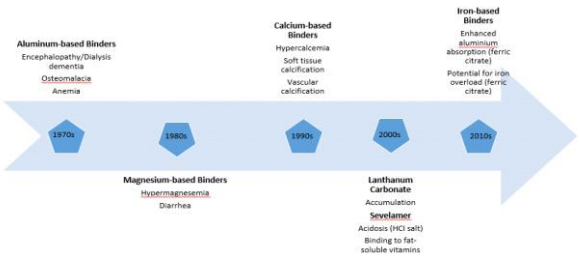
INTRODUCTION

Elevated levels of phosphorus in the blood are a significant factor that can predict cardiovascular disease and mortality in individuals with advanced stages of chronic kidney disease, regardless of other contributing factors. This phenomenon arises from the kidney's diminished ability to eliminate phosphate from the body. [1, 2, 3]

The mortality attributed to cardiovascular disease (CVD) among patients with end-stage kidney disease (ESKD) has risen, comprising 51% of known causes of death in 2011 to 2013 and increasing to 53% and 55% of known causes among patients undergoing peritoneal and hemodialysis, respectively, in 2018.[4] Novel therapies are needed to improve cardiovascular health in patients with CKD & ESRD. Enhancing the management of phosphate levels presents a logical strategy for enhancing cardiovascular health, as retaining phosphate and experiencing elevated phosphorus concentrations can lead to various physiological disturbances associated with an elevated risk of cardiovascular disease. Elevated levels of phosphate contribute to endothelial dysfunction, resulting in cell damage through the initiation of endothelial cell apoptosis and the disturbance of mitochondrial function. [5]

This condition is usually controlled using phosphate binders taken orally alongside limitations on dietary phosphate intake. These medications work towards decreasing serum phosphate levels by diminishing the absorption of dietary phosphate in the intestines.[3] Hyperphosphatemia typically doesn't present noticeable symptoms. Nevertheless, phosphate binders can offer relief from red irritated eyes and pruritus, symptoms more frequently observed in patients with serum phosphate levels exceeding 1.8 mmol/L.[6,7]

Phosphate binders can constitute a significant portion, up to half, of the daily pill burden for individuals suffering from chronic kidney disease. [8] Coupled with common adverse drug reactions, especially gastrointestinal discomfort, this adds to the challenge of maintaining consistent medication adherence. [9]



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Types Of Phosphate Binders

There are three primary categories of phosphate binders: calcium-based and aluminum-based binders, which have been in use for an extended period and are cost-effective, and the newer non-calcium-based binders (such as sevelamer, lanthanum, and sucroferric oxyhydroxide), which are notably more costly.[1,2,10]

Calcium carbonate is frequently prescribed as the predominant type of phosphate binder, especially in cases of chronic kidney disease where dialysis is not required. [3] It is commonly administered to individuals with advanced chronic kidney disease, including those undergoing dialysis. Similar to other phosphate binders, calcium-based ones demonstrate optimal effectiveness when taken alongside meals, which also helps limit calcium absorption.[11] These medications should be recommended alongside moderate dietary phosphate restriction, ideally under the supervision of a qualified dietician. It's advisable to steer clear of phosphate-rich foods with a high phosphate to protein ratio, such as processed foods, fast foods, and cola drinks. Conversely, foods with a high biological value, like meats and eggs, should be prioritized to sustain nutritional levels. [12, 13] In cases of non-dialysis chronic kidney disease, aluminum-based binders are considered as a second-line drugs. The other newer non-calcium-based binders, namely sevelamer, lanthanum, and sucroferric oxyhydroxide, are also available as alternatives.

With the exception of lanthanum and sucroferric oxyhydroxide, the initial dosage for all binders usually ranges from 1 to 2 tablets taken three times a day with meals, varying based on their potency, half a tablet is commonly used to cover between-meal snacks. For calcium-based binders and sevelamer, the dosage can be escalated to a maximum of six or more tablets per day if necessary. It's important to administer other medications separately, as phosphate binders may disrupt the absorption of drugs like oral iron and ciprofloxacin. [14,15]

Calcium Acetate or Calcium Carbonate for Hyperphosphatemia of Hemodialysis Patients-

Phosphate binders, including non-calcium-based phosphate binders and calcium-based phosphate binder, are widely used to lower serum phosphorus levels in CKD patients and prospective cohort study proved that treatment with phosphorus binders was independently associated with improved survival among incident hemodialysis patients.[16] Recently non-calcium-based phosphate binders slight superior to calcium-based phosphate binders on mortality reduction in CKD patients. However, in developing countries, non-calcium-based phosphate binders (sevelamer and lanthanum carbonate) are not easily available for their high prices, and calcium carbonate and calcium acetate remain to be the most commonly used phosphate binders.[17]

Treatment-related adverse effects: The most common side effects reported were gastrointestinal symptoms, including epigastrium pain, bloating, nausea and anorexia. There was a trend of higher incidence of adverse gastrointestinal events in calcium acetate treated patients compared with calcium carbonate treated patients.

Hypercalcemia*:* There was no significant difference for the incidence of hypercalcemia between calcium acetate group and calcium carbonate group.

The main side effects of both agents were gastrointestinal symptoms, including epigastrium pain, bloating, nausea and anorexia. There was a trend of higher incidence of adverse gastrointestinal events in calcium acetate group and that might lead to the higher incidence of treatment intolerance of calcium acetate. Those most reported symptoms related to the two agents disappeared after treatment withdrawal. Another announced side effect was agents relating to hypercalcaemia. Calcium acetate showed better effect on hyperphosphatemia control than calcium carbonate, but with a relative higher incidence of intolerance.

Using calcium acetate instead of calcium carbonate can effectively manage hyperphosphatemia in patients with end-stage renal disease (ESRD). By employing acetate, it's possible to control hyperphosphatemia with significantly lower doses of calcium, potentially reducing the risk of hypercalcemia.[18]

Sevelamer Hydrochloride & Sevelamer Carbonate for Hyperphosphatemia of Hemodialysis Patients

When managing hyperphosphatemia with sevelamer hydrochloride, it was found to exacerbate metabolic acidosis more than calcium carbonate. Sevelamer, whether hydrochloride or carbonate, works by decreasing the quantity of bioavailable phosphorus derived from dietary intake and absorbed from gastrointestinal fluids. In individuals with normal kidney function, any irregularities in phosphorus absorption in the intestines are offset by effective urinary phosphorus excretion, maintaining normal phosphorus levels (normophosphatemia). However, as kidney function declines in advanced renal failure, the inefficient or absent phosphorus excretion fails to counterbalance the continuous intestinal absorption of phosphorus, resulting in hyperphosphatemia.

Examining the clinical data available on sevelamer carbonate, it has been shown to be equally effective as sevelamer hydrochloride in reducing serum phosphorus levels and lipid levels in two separate studies. One study involved end-stage renal disease (ESRD) patients undergoing hemodialysis, while the other study involved patients with chronic kidney disease (CKD) who were not undergoing dialysis.[22]

Sevelamer hydrochloride was the first phosphate binder without aluminium or calcium (metal free) developed specifically for treating hyperphosphatemia in end-stage renal disease (ESRD). Sevelamer carbonate was created as a substitute for sevelamer hydrochloride with the aim of enhancing its buffering capacity.

This novel phosphorus-binding medication presents the opportunity for enhanced gastrointestinal tolerance and the possibility of alternative formulations, such as a powder, which could enhance adherence to binder therapy. By merely altering the accompanying counterion, the buffering capacity of sevelamer hydrochloride was enhanced, leading to a statistically notable improvement in serum bicarbonate levels among individuals with chronic kidney disease undergoing hemodialysis.[23]

Iron-Based Phosphate Binders In Reduction Of Hyperphosphataemia In Chronic Kidney Disease Patients

Phosphate binders, along with dietary phosphate restriction, have traditionally been the primary and cost-effective approach for managing hyperphosphatemia in patients with CKD stage 3 and beyond. However, they have become less favoured due to concerns regarding calcium toxicity.[19] Ferric citrate is an orally administered phosphate binder that does not contain

calcium. It offers a dual advantage of lowering serum phosphate levels and boosting hemoglobin levels by replenishing iron stores.[20]

The utilization of ferric citrate among non-dialysis dependent CKD patients in stages 3, 4, and 5 led to notable decreases in serum phosphate levels and enhancements in hematological indicators such as hemoglobin, iron, ferritin, total iron binding capacity, and transferrin saturation. Additionally, the study revealed that ferric citrate was well-received, with only minimal and mild gastrointestinal adverse events reported.

In contrast to individuals undergoing hemodialysis, non-dialysis dependent CKD patients retain some level of kidney function, allowing for the excretion of a certain amount of phosphorus.[21] Ferric citrate demonstrate effective control of hyperphosphatemia in adult CKD patients undergoing hemodialysis, with comparable efficacy to sevelamer carbonate. The treatment's safety profile is favourable, with most treatment-emergent adverse events being mild and well-tolerated by patients.

CONCLUSION

In conclusion, the use of iron-based phosphate binders with significant iron absorption properties could represent a novel paradigm for correcting anemia and hyperphosphatemia in CKD patients. Newer iron-containing phosphate binders have potential benefits, such as lower pill burden (sucroferric oxyhydroxide) and improved iron parameters (ferric citrate). The biggest challenge to phosphate binder efficacy is non-adherence. Novel iron-containing phosphate binders are efficacious both in terms of hyperphosphatemia control and reduced ESAs and IV iron needs for anemia management among patients with CKD. However, previous animal experiments and clinical studies have shown that high-dose iron administration via the oral route can cause iron overload, even in the presence of high hepcidin levels, unable to block iron absorption as efficiently as generally thought.

Finally, there is an urgent need to know more about possible safety hazards with iron-containing phosphate binders. In particular, more information is required on whether ferric citrate induces oxidative stress to the same extent or not as high-dose IV iron. No long-term safety data on hard outcomes in patients with CKD are so far available with ferric citrate. However, that this is also true for IV iron administration in general to such patients. Future randomized prospective cohort studies are necessary to address these important issues.

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