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Oral Phosphate Binders: Hyperphosphatemia Treatment in Chronic Kidney Disease

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Abstract
Hyperphosphatemia is a disorder of mineral metabolism in chronic kidney disease that caused by decreased kidney ability to excrete phosphate. It is potentially life threatening by contributed to the development of mineral bone disease and cardiovascular calcification. Those complications prevented by diet restriction, used of phosphate binders and hemodialysis and must be done simultaneously to be able to control normal phosphate levels, thus risk of morbidity and mortality can be decreased. Oral phosphate binders is used to inhibit absorption of phosphate in gastrointestinal, which derived from phosphate intake. The currently available oral phosphate binding agents have their respective deficiencies and none of them have become superior among others inspite of a progressive development of phosphate binding agents. Effectiveness of these agents which is associated with phosphate binding capacity, depends on pH in gastrointestinal. Therefore, these agents should be used at the right time.

Keywords: *Oral Phosphate Binders, Hyperphosphatemia, Chronic Kidney Disease*

I. INTRODUCTION

Normal kidney have an important role in the calcium-phosphate homeostasis and related hormones such as parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23). In chronic kidney disease (CKD), these homeostasis is disturbed because phosphate excretion decrease along with impaired renal function. Therefore, serum phosphate levels rise and cause a progressive hyperphosphatemia. Uncontrolled hyperphosphatemia in CKD patients will increase the risk of renal osteodystrophy through secondary hyperparathyroidism mechanism. Hyperphosphatemia is also a trigger of calcification vascular which can develop into complications of cardiovascular disease. In order to maintain serum phosphate levels, used of oral phosphate binders are required besides dietary restriction of phosphate and current dialysis modalities. Unfortunately, the benefit of current phosphate binders have not achieved the recommended range yet. Hence, biopharmaceutical development of this agents still continue to be done.

II. PHOSPHATE REGULATION IN KIDNEY

Phosphate is an important component of hydroxyapatite which is the main constituent of bone mineral, nucleic acid, protein bioactive signal, phosphatilation enzyme and cellular membrane. In the body, the concentration of phosphate in bone is 85%, soft tissue 14% and the rest is distributed among other tissues and extracellular fluid (Fenton & Praetorius, 2016). The phosphate homeostasis is maintained by the intestines and kidneys through regulation of absoption, excretion and reabsorption. When serum phosphate concentrations decrease as a result of reduced intake, there will be increased ionized calcium concentration, decreased PTH secretion and decreased phosphate excretion in the kidney. At the same time, renal activity of 25-hydroxyvitamin D 1α-hydroxylase, 1,25-dihydroxi vitamin D synthesis, intestinal phosphate absorption and reabsorption in the kidneys increase. Meanwhile, the calcium concentration will decrease when intake phosphate increase and all effects go the opposite. By all these effects, the serum phosphate concentration will return at a nomal range. Phosphatonin, FGF-23, and serum frizzled-related protein 4 (sFRP-4) work by modulating phosphate reabsorption in the kidneys, decreasing insulin-like growth factor 1 (IGF-1) activity, and increasing the activity of 25-hydroxyvitamin D 1α-hydroxylase (Murer, Biber, & Wagner, 2016).

In the filtration process (Figure 1), all phosphate in the serum is filtered in the glomerulus. Beyond normal intake phosphate and intact parathyroid glands, 20% of the filtered phosphate is excreted and the remaining 80% reabsorption in the renal tubule. The proximal tubule is the main phosphate reabsorption site along the nephron. While in the proximal straight tubule and the beginning of the distal tubule, it is only able to reabsorb phosphate in small amounts. The transport speed of phosphate in the convoluted proximal tubule is 3 times faster than the proximal straight tubule. Uptake phosphate in the proximal tubule is mediated by co-transport Na-phosphate (NaPi IIa and NaPi IIc) located in the apical border of proximal tubular cells. Both co-transport of Na-phosphate are homologous and are thought to have the same structure (Fenton & Praetorius, 2016).

III. PATHOPHYSIOLOGY OF HYPERPHOSPHATEMIA

The main pathophysiology of hyperphosphatemia in CKD is the decreased of the kidneys ability to excrete phosphate. In physiological conditions, phosphate excretion depends solely on the renal excretion function expressed in the glomerular filtration rate (GFR). This condition will lead to phosphate retention and elevated serum phosphate levels. In the early stages of CKD, the decrease in GFR and serum phosphate levels increase will be compensated by a counter regulatory mechanism of PTH and FGF 23. As the phosphate level increases, both of these hormones will also increase and activate the NaPi2a phosphate transporter in the proximal apical membrane. This adaptation will increase the amount of phosphate carried through the proximal tubular segments thereby causing phosphaturia. The counter regulatory mechanisms of these two hormones will be maladaptive at a certain level of improvement, because they are insufficient to normalize the phosphate levels (Figure 1). Thus, serum phosphate levels, PTH and FGF-23 levels will continue to increase and are at risk of causing other complications such as cardiovascular disease and bone mineral disorders that can worsen the prognosis of CKD (Vervloet, Sezer, Massy, Johansson, & Cozzolino, 2016).

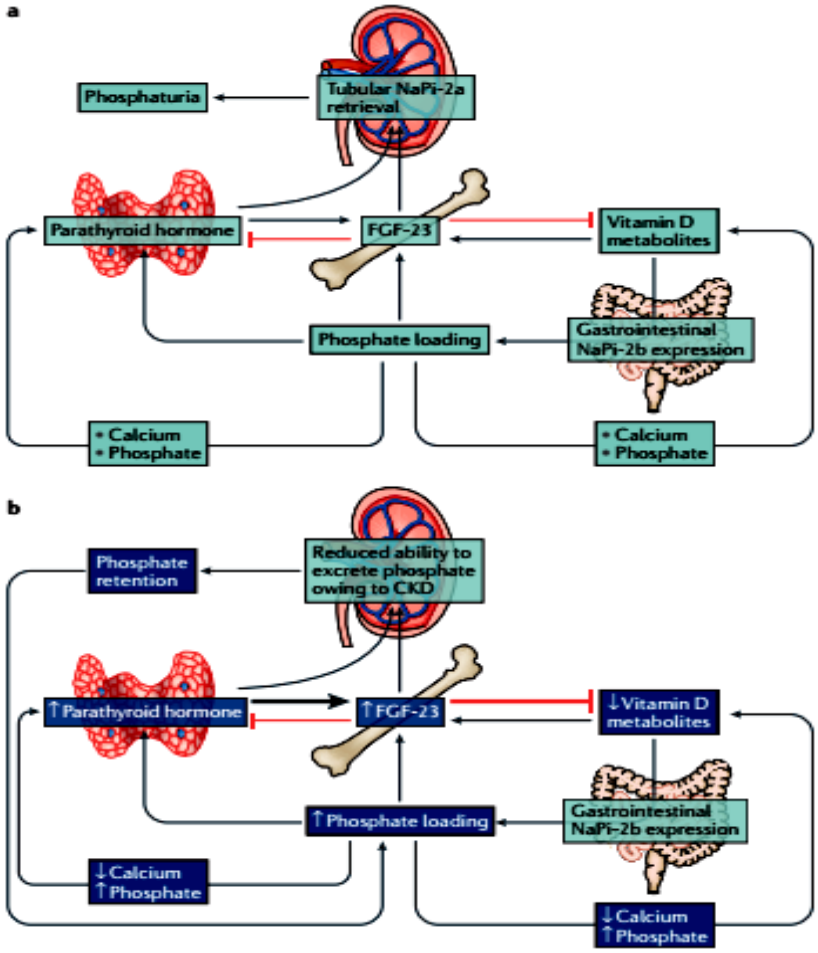

Figure 1. (a) Phosphate regulation in the normal renal function; (b) Disorder phosphate balance in the impaired renal function (Vervloet, Sezer, Massy, Johansson, & Cozzolino, 2016).

IV. COMPLICATION FROM HYPERPHOSPHATEMIA

Hyperphosphatemia supported by hypocalcaemia, increased calcium-phosphate products and decreased vitamin D synthesis, will result in secondary hyperparathyroidism. Metabolic changes of these minerals are part of the connecting pathway associated with mineral and bone disorders. In addition, other risks that may occur in patients with renal failure are cardiovascular calcification.

a. ***Mineral and bone disorders:*** Imbalances of calcium and phosphate metabolism will result in demineralization of bone that may lead to fracture (Akhtar & Gonzales, 2004). Under normal circumstances, parathyroid hormone will be anabolic to the bone, but will turn to catabolic when the level exceeds normal (Silver & Bushinsky, 2004). These conditions generally occur in patients with CKD as a result of stimulation of osteoclast action in dissolving bone and cause fracture. This process is highly progressive and generally "silent" clinically until there is small

injury that can cause pathologic fractures to emerge (Friedman, 2005). Criteria of mineral and bone disorders include (KDIGO, 2009).

b. Cardiovascular calcification: Vascular calcification is one of the arteriosclerotic markers and arterial stiffness, which is often found and may increase the risk of mortality in hemodialysis patients. The prevalence of coronary heart disease and left ventricular hypertrophy in patients with renal failure is quite high at 45% and 75%. This consequence occurs through the mechanism of calcium mobilization with bone so that a person with a lot of coronary calcification usually has reduced bone mass (Friedman, 2005). Patients with renal failure will be at risk of calcification in the event of an increase in calcium-phosphate products, phosphate levels (> 6.5 mg / dL) and parathyroid hormone. Meanwhile, the level of calcium and the use of phosphate binding agents with calcium preparations is not a risk factor for cardiovascular disease (Ganesh, Stack, & Levin, 2001).

V. MANAGEMENT OF HYPERPHOSPHATEMIA

In the condition of CKD, hyperphosphatemia is very important to treat because if not resolved it will cause secondary hyperparathyroidism, renal bone disease, vascular calcification, increase morbidity and mortality. Thus, control efforts are important to do even though no studies have shown that decreasing serum phosphate can increase the life expectancy of CKD patients. In the management of hyperphosphatemia, there are three main things to note: (1) dietary restriction, (2) administration of oral phosphate binder and (3) adequate dialysis. All three must be done simultaneously to be able to control normal phosphate levels (Hutchison, 2009).

VI. ORAL PHOSPHATE BINDERS

All of the currently available oral phosphate binding agents have their respective deficiencies and none have become superior among others. Nevertheless, there is a progressive evolution of phosphate binding agents starting from aluminum and calcium salts and new classes of agents such as sevelamer, lanthanum and iron based phosphate binder (Hutchison, 2009).

a. Aluminum-based binder: Aluminum-based binders are widely used for the control of hyperphosphatemia in ancient times around the 1970s-1980s. This class of agents has been shown to be very effective in lowering serum phosphate levels by two mechanisms (1) forming a coordination compound with phosphate ions so that the phosphate is trapped (2) forming a precipitated aluminum phosphate in the gut that is insoluble and nonabsorbed. However, although effective, the use of this long-range range is not recommended by KDIGO due to its accumulated and toxic properties in cerebral and bone tissue and causes osteomalacia and encephalopathy (Hutchison, 2009).

b. Calcium-based binder: In 1980, it introduced and marketed a new oral phosphate binder based on calcium salts which is effective and well tolerated. As for several different formulations of calcium carbonate, calcium acetate and calcium citrate. Calcium citrate shouldn't be used by CKD patients undergoing dialysis because citrate can facilitate absorption of aluminum in the intestinal. Whereas calcium acetate having P binder coefficients that are relatively similar to calcium carbonate can provide the same control over hyperphosphatemia but with smaller elemental doses. However, some guidelines currently provide warnings regarding the use of calcium-based binder groups in order not to give high doses and be wary of possible side effects. This class of agents has a positive induction effect on calcium equilibrium that can result in osteoarthritis of thyroid, adynamic bone disease and vascular calcification (Hutchison, 2009).

c. Sevelamer hydrochloride / carbonate: Sevelamer hydrochloride (HCl) is an anion exchange resin commonly used as an aluminum-free and calcium-free phosphate binder. Efficacy of decreased blood phosphate levels was recognized by KDIGO in 2003. Sevelamer also contains many amine groups separated by one carbon from the polymer chain. The amine group will be protonated in the gut and then bind to phosphate by ionic and hydrogen bonds. The advantages of this class of agents are (1) can reduce calcium overload in patients undergoing hemodialysis; (2) have a pleiotropic effect that lowers serum lipid levels and anti-inflammatory activity. The disadvantage is the large size of the pill and can decrease the patient's adherence to taking the drug. Sevelemer carbonate is a new formulation of the drug class of sevelamer. Like the HCl sevelamer, it is also an anion exchange resin that has good control over acid-base status and decreased metabolic acidosis but the gastrointestinal effect is smaller than that of HCl (Hutchison, 2009).

d. Lanthanum carbonate: Lanthanum carbonate (LC) is another binder phosphate that is not based on aluminum and calcium besides sevelamer. This drug has been available in the United States since 2005 and in the EU in 2006. In preclinical studies in animals, it has been suggested that lanthanum may have an effect similar to that of aluminum-based binders and twice that of calcium based binders, is better (Hutchison, 2009).

e. Iron-based binder: Iron (III) -oxyhydroxide or sucroferric oxyhyroxide is a calcium free phosphate binder and derived from a mixture of polynuclear Iron (III) -oxyhydroxide, sucrose and starch. This iron-based mechanism is to exchange hydroxyl ligands owned by sucroferric with phosphate in the diet so that phosphate is bound and can be eliminated through the feces. Sucroferric oxyhydroxide can work efficiently at any physiological pH (pH 1.2-7.5), but because uptake iron is quite high in fasting conditions it is recommended at the same time as feeding (Cernaro, et al., 2016).

VII. PHOSPHATE BINDING CAPACITY COMPARISON OF PHOSPHATE BINDERS

As mentioned previously, phosphate binding agents work to inhibit phosphate absorption in the gastrointestinal tract where the pH atmosphere affects effectiveness. Therefore, the bonding capacity of the drug depends heavily on the appropriateness of drug use by paying attention to its drinking time. In the Yaguchi et al. Study, observations were made on the bonding capacity of phosphate binding agents in several different pHs representing gastrointestinal atmosphere of pH 2, 5 and 8. The phosphate binding agents used in the study were calcium carbonate, sevelamer, lanthanum, ferric citrate and PA21. The 5 agents exhibit a bonding profile (Figure 2) varying at different pH (Yaguchi, et al., 2015).

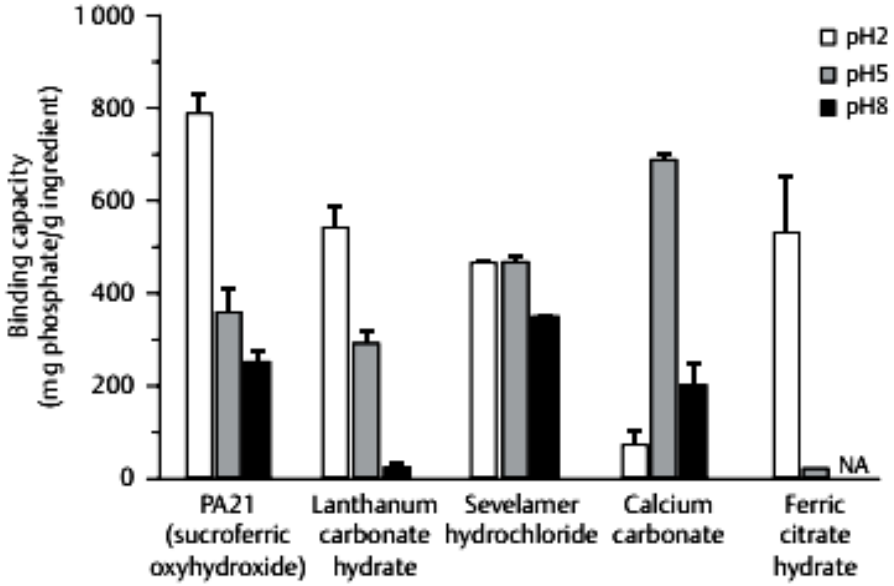

Figure 2. Phosphate Binding Capacity in different gastrointestinal pH (Yaguchi, et al., 2015).

At pH 2, agents that have high binding capacity to phosphate are PA21 (800 mg / g of food) followed by ferric citrate (550 mg / g food), lanthanum (550 mg / g food), and sevelamer (500 mg / g of food), while the calcium carbonate binding capacity at low pH2 (100 mg / g of food). Furthermore, at pH 5, the drug having the highest binding capacity to phosphate was calcium carbonate (700 mg / g food), followed by sevelamer (500 mg / g food), PA21 (350 mg / g food), lanthanum (300 mg / g food) and the last ferric citrate (<100 mg / g food). At pH 8, agents that have a high enough bonding capacity are sevelamer (350 mg / g food), PA21 (250 mg / g food) and calcium carbonate (200 mg / g food), whereas lanthanum has only <100 mg bonding capacity / g of food and ferric citrate have absolutely no binding capacity at this pH (Yaguchi, et al., 2015).

The results of this study provide information that at higher pH that is in the small intestine and colon, the lanthanum and ferric citrate bond capacity is very small. In calcium carbonate, the highest phosphate bonding capacity is at pH 5, this is because the dissociation of calcium carbonate into solution to release calcium ions will increase at higher pH of the gastrointestinal tract. However at a very high pH the solubility decreases, so at pH 8 the amount of calcium in the form of ions is not much and the bond capacity is greatly decreased. From these profiles, it can be seen that the

sensitivity of the drug is affected by changes in the pH of the gastrointestinal tract. The order of sensitivity of phosphate binding agent from the lowest to the highest was sevelamer (1,3), PA21 (3,1), calcium carbonate (9,6), lanthanum (21,7) and ferric citrate (> 23,6) (Yaguchi, et al., 2015).

In addition to the effect of pH on phosphate binding capacity, this study also looked at the effect of the magnitude of intake phosphate on the ability of the phosphate binding agent to maintain normal serum phosphate levels. Sevelamer and PA21 showed significant suppression at doses of 500 mg / kg and 250 mg / kg in all pH situations. Lanthanum had significant suppression at 250 mg / kg at pH 2 but was not significant at pH 5 and 8. Calcium carbonate showed significant suppression at 500 mg / kg and 250 mg / kg in pH atmosphere 2 and 5 but not significant at pH 8 Ferric citrate showed significant suppression at 500 mg / kg and 250 mg / kg in a pH 2 atmosphere but not at pH 5 and 8. From these results it can be seen the efficiency of suppression of phosphate binding agents on levels of elevated serum fofat levels in various pH digest. The efficiency profile of the phosphate binding agents can be seen in Table 1. (Yaguchi, et al., 2015).

The cause of differences in the efficiency of suppression occurring in the binding agent is not yet known, but it is thought that the adsorption of other compounds other than phosphate may interfere with the binding of the drug to phosphate so that the efficiency of suppression may decrease. In lanthanum and ferric citrate, the efficiency of in vitro and in vivo suppression is known to have the same result, but on the calcium carbonate the results are different. This can be due to the equilibrium between bonding capacity and drug solubility changing at a certain pH can decrease the efficiency of suppression. Another influential factor is the possibility of the relative transfer rate of this drug from the stomach to the duodenum altered by the presence of foods that alter the pH of the gastrointestinal tract. Therefore the time to take calcium use should be taken into account to prevent the instability of this drug (Yaguchi, et al., 2015).

Table 1. Suppression efficiency of each phosphate binders after phosphate intake (Yaguchi, et al., 2015)

Types of phosphate binder		PA21		Lantanum		Sevelamer		Calcium carbonate		Ferric citrate	
Dose		250 mg/kg	500 mg/kg	250 mg/kg	500 mg/kg	250 mg/kg	500 mg/kg	250 mg/kg	500 mg/kg	250 mg/kg	500 mg/kg
Amount of ingredient (mg/kg)		55	110	65	130	103	205	100	200	45	90
Suppression efficiency (%)	pH 2	33,4	76,3	37,6	66,7	33,1	41,3	63,7	65,4	39,9	55,3
	pH 5	42,2	98,6	35,6	31,2	38,3	46,0	49,8	63,0	36,9	29,3
	pH 8	30,8	71,8	19,5	24,0	42,1	49,6	36,4	42,9	31,5	35,7

VIII. CONCLUSION

Hyperphosphatemia in chronic kidney disease contributes to an increased risk of patient morbidity and mortality associated with a prognosis of mineral bone disease and cardiovascular calcification. Therefore, multimodal therapy should be performed simultaneously to be able keeping phosphate levels of ckd patients remain in the normal range. Used of oral phosphate binder is essential to decrease the amount of phosphate from food that enters the body through the gastrointestinal. Each agents has different phosphate binding capacity and optimal pH to be effective, which can be considered in the choice of appropriate therapy for patients.

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