Review Article:

Phosphate Binders in CKD: "New Kids on the Block"

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Abstract:

Phosphate control is essential component of dietary and medical management of chronic kidney disease (CKD) patients. Hyperphosphatemia has a significant effect on morbidity and mortality of CKD patients. This review takes us through the different older and newer medications available for management of hyperphosphatemia.

Key words: *Hyperphosphatemia, lanthanum, kayexalate, sevelamer hydrochloric acid, sevelamer carbonate, aluminum hydroxide, Ferric citrate, sucroferric oxyhydroxide.*

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Introduction:

Phosphate control is essential component of dietary and medical management of chronic kidney disease CKD) patients. The tendency toward phosphate retention develops early in chronic kidney disease when GFR<60ml/min/1.73m2 due to the reduction in the filtered phosphate load. Overt hyperphosphatemia is evident when the estimated glomerular filtration rate (eGFR) falls below 25 to 40 mL/min/1.73 m^2 [1, 2]. Hyperphosphatemia has been associated with increased mortality and morbidity and mortality [3]. Phosphate binders are the cornerstone in the management of hyperphosphatemia in CKD and dialysis patients.

Past-Present-Future:

Phosphate-binding compounds were introduced in the 1970s for the treatment of hyperphosphatemia in patients on dialysis after it was observed that oral administration of aluminum hydroxide as an antacid also reduced serum PO4 levels [4]. Calcium-based binders (calcium bicarbonate and calcium acetate) became the binder of choice in the 1980s and 1990s.These calcium containing phosphate binders were not associated with encephalopathy or bone disease commonly seen with aluminum containing binders but there use is associated with cardiac and metastatic calcification [5].Later there was addition of non-calcium containing binders sevelamer hydrochloride and lanthanum carbonate. Iron containing phosphate binders: ferric citrate and sucroferric oxyhydroxide are latest addition to the group of phosphate binders. They are unique because they replete body iron stores in addition to binding phosphate

CKD-Non-Dialysis patients:

In pre-dialysis CKD patients, aim is to maintain the serum phosphate level in the normal range (i.e., <4.5 mg/dL [1.45 mmol/L]); this level is consistent with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [5,6].Hyperphosphatemia is a stimulus for hyperparathyroidism Hyperphosphatemia has been associated with increased mortality among pre-dialysis CKD patients [7]. Progressive or persistent hyperphosphatemia >4.5 mg/dL is an indication for treatment. Phosphate restriction <900mg/day and use of phosphate binders to decrease gastric absorption is primary treatment used in non-dialysis CKD population [8].

ESRD-Dialysis patients:

In dialysis patients, aim is to keep phosphate in normal range between 3.5-5.5 mg/dl in line with KDOQI guidelines [9]. Phosphate level>5.5mg/dl is an indication for treatment. A meta-analysis of 12studies including 92,345 patients with CKD, over 97 percent of whom were on dialysis showed increased mortality with phosphate>5.5mg/dl [10]. Moderate dietary phosphate restriction around 900mg/day without compromising nutritional status is consistent with the KDOQI and KDIGO guidelines. Two observational studies have suggested that phosphate binders are associated with decreased mortality among dialysis patients [11,12], however randomized controlled trials are needed to determine whether the use of phosphate binders provides a benefit on clinically important endpoints among dialysis patients.

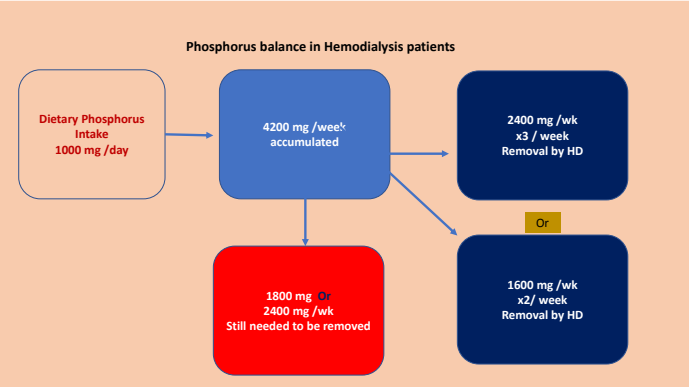

Figure 1: Phosphorus balance in maintenance hemodialysis patients undergoing thrice a week or twice a week hemodialysis

Types of Phosphate Binders:

Calcium containing phosphate binders*: *(Calcium carbonate & Calcium acetate)

Calcium acetate is more effective than calcium carbonate in binding phosphate in GI tract and lowering serum phosphate [13]. They are only effective when taken with meals. The amount of elemental calcium contained in the phosphate binder should not exceed 1500 mg per day. This is consistent with both the KDOQI and KDIGO guidelines [5]. Calcium-containing phosphate binders may predispose to extra skeletal calcium phosphate deposition, particularly in the setting of hyperphosphatemia [14,15].This is a particular problem among patients who are on both calcium-containing phosphate binders and active vitamin D analogs. In such patients who develop hypercalcemia, the dose of the calcium-containing phosphate binder should be decreased [5] In addition, the dose of active vitamin D analogs should be lowered or discontinued until calcium levels return to normal.

Non-Calcium containing phosphate binders (Sevelamer hydrochloride, sevelamer carbonate & Lanthanum carbonate)

These are nonabsorbable cationic polymers that bind phosphate through ion exchange, both taken thrice daily with meals. A number of trials have suggested that non-calcium-containing phosphate binders, compared with calcium-containing phosphate binders, decrease mortality among CKD patients [16]. High cost is a major drawback

Iron containing phosphate binders

Sucroferric oxyhydroxide

It is a chewable phosphate binder, appears to be comparable with sevelamer in efficacy and safety and may be associated with a lower pill burden [17]. Dose is 2.5 g three times daily with meals or, if dosing is expressed in terms of elemental iron, 500 mg three times daily with meals. Adverse effects are primarily gastrointestinal (diarrhea, nausea, abnormal product taste, constipation, and vomiting).

Ferric citrate

It is the latest edition to the class of phosphate binders available with the name of '**Nephryxia**' (Nephrocare) in Pakistan (Auryxia in USA). This is our "new kid on the block". Each 1 gram tablet contains 210 mg of ferric iron, which is equivalent to 1 g ferric citrate. In the GI tract, ferric iron binds with phosphate to create ferric phosphate, which is insoluble and excreted [18]. The recommended starting dose for ferric citrate is 1-2 tablets three times per day with each meal with titration every 1 to 2 weeks based on serum PO4 levels until target range is reached, up to a maximum dose of 12 tablets daily. It in effective in reducing serum phosphate concentration and increases serum iron simultaneously [19].Ferric citrate increases GI absorption of aluminum predisposing to aluminum toxicity

Other phosphate Binders:

Nicotinamide metabolite of nicotinic acid (niacin, vitamin B3), may lower phosphate levels by reducing gastrointestinal tract phosphate absorption [20].

Tenapanor is an inhibitor of intestinal sodium/hydrogen exchanger 3 (NHE3) that lowers serum phosphorous by blocking its Para cellular transport from the intestinal lumen [21]. Adverse effect include increase in stool frequency.

Aluminum Hydroxide

Aluminum-based phosphate binders are associated with aluminum toxicity, should be avoided in all patients of CKD except for short-term therapy of severe hyperphosphatemia. There is no safe but effective dose of aluminum hydroxide in CKD

Calcium citrate

Is a phosphate binder that binds phosphate in GI tract preventing its absorption? The use of calcium citrate has been associated with aluminum neurotoxicity caused by increased intestinal aluminum absorption and the rapid onset of symptomatic osteomalacia. It should be avoided in all CKD patients [22].

Types of Phosphate Binders available in Pakistan:
Commonly available phosphate binders with brand names, prices and comments

Class of Phosphate Binder	Drugs	Common Names	Dose	Price (PKR)	Comments
Calcium containing binder	Calcium acetate (667mg)	Phoslow Lophos Phoslo	1-4×TDS with meals	4.0/tab	Better binding capacity & less calcium load
	Calcium carbonate (1250mg)	Qalsan D Chewcal D	1-3×TDS with meals	3.5/tab	OTC available
Non-calcium phosphate binder	Sevelamer HCL (400mg)	Salver Renavel	1-4×TDS with meals	35/tab 35/tab	Can cause NAGMA in CKD
	Sevelamer bicarbonate (800mg)	Renvella Selcarb	1-4×TDS with meals	70/tab	No risk of metabolic acidosis
Iron containing phosphate binder	Ferric citrate (210mg)	Nephryxia	1-4×TDS with meals	15/tab	Correct iron deficiency too. May need to reduce IV iron

Table 1: Commonly available Phosphate binders in Pakistan along with the brand name and prices.

Summary of Key Features of Phosphate Binders:

- The optimal control of phosphorus levels remains difficult in chronic kidney disease patients.
- Oral phosphate binders can help lower phosphorus levels, but safety and tolerability issues must be considered when selecting which one to use.
- **Aluminum** is associated with potentially serious toxic risks.
- **Calcium-based** binders are effective and widely used, but can lead to hypercalcemia and/or positive calcium balance and progression of cardiovascular calcification.
- **Lanthanum** is an effective binder which can reduce the progression of vascular calcifications.
- The **resin-based binders**, sevelamer carbonate, have profiles that may lead to reduced or no progression of vascular calcifications. Their main side effects are gastrointestinal in nature.
- **Iron-based binders** could be of clinical importance. In CKD patients not on dialysis, ferric citrate could obviate the need for extra oral iron administration and possibly favor compliance.
- **New agents**, which inhibits the active intestinal phosphate transport, are studied as add-on therapy to classic phosphate binders in patients with moderate-to-severe CKD and in patients on dialysis

Table 2: Key features of phosphate binders available for use in the market.

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