

The Role of Phosphate Binders in the Treatment of Chronic Kidney Disease

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Abstract: *In end stage chronic kidney disease hyperphosphatemia is an unavoidable consequence present in the majority of dialysis patients. Existing dialysis prescription pattern and dietary restriction of phosphate are not enough to uphold serum phosphate levels within the suggested range so that the majority of dialysis patients necessitate oral phosphate binders. Regrettably, conventional phosphate binders are linked with a range of limitations and side effects and are not consistently effective. Eventhough phosphate binders are known to reduce serum phosphate levels in patients, it remains indecisive whether they improve clinical outcomes. Calcium based salts are effective, economical and most widely used, but nowadays their connection with hypercalcemia and vascular calcification is a matter of concern. Though highly efficient Aluminium-containing agents are no longer widely used because of well known and proven toxicity. The non calcium based phosphate binders- Sevelamer hydrochloride and lanthanum carbonate is associated with fewer adverse effects. The restricting factors for its wider use is the large pill burden and high cost. In addition, there is a debatable fact about the efficacy of sevelamer as a monotherapy in lowering phosphate to target levels in severe hyperphosphatemic conditions. The main reasons which contributes to poor medication adherence are the large pill burden and adverse effects of the phosphate binders.*

1. Introduction

Hyperphosphatemia is a predictable consequence of chronic kidney disease (CKD). It is seen in majority of dialysis patients and continues to epitomize a major challenge to clinical nephrologists.^[1] Indeed more than 53% of Indian haemodialysis patients have plasma phosphate of ≥ 1.8 mmol/L (5.5 mg/dL) regardless of prescription of oral phosphate binders and dietary manipulation^[1]. Normal kidneys filter large amounts of organic phosphate and more than 90% is reabsorbed by the renal tubules^[2]. Early renal dysfunction reduces filtered phosphate but also decreases tubular reabsorption, and in such a way the urinary phosphate excretion continues to be equivalent with GI absorption.^[2] As a result, the net balance between phosphate input and output is maintained for a period of time with a small change in serum phosphate levels. The renal function deteriorates further, this homeostatic mechanism fails resulting in progressive hyperphosphatemia. and positive phosphate balance. Untreated hyperphosphatemia can lead to renal osteodystrophy, SHPT, increased morbidity and mortality and vascular calcification.^[3]

Accordingly, in the management of CKD phosphate control remains an important therapeutic target, not only to reduce the risk of vascular calcification and cardiovascular mortality but also to halt the progression to secondary hyperparathyroidism.^[10] Unfortunately, over the past two decades phosphate control has not been considerably improved.^[11] Factors including phosphate binder prescriptions, the difficulty of adhering to renal diets, and insufficient phosphate clearance by dialysis have contributed to this. Adding up factors such as safety, palatability, cost, tolerability, and efficacy are also important (Table 1).^[12]

Table 1 Suggested characteristics of an ideal oral phosphate binder

High affinity for binding phosphate – low dose (pill burden) required
Rapid phosphate binding regardless of ambient pH
Low solubility
Low systemic absorption (preferably none)
Non toxic and without side effects
Solid oral dose form
Palatable – encourages compliance
Inexpensive

Phosphate Binders

The three main types of phosphate binders available are calcium-containing binders and aluminium containing binders. These have been around for many years and are cheap. The new non-calcium-based binders (sevelamer, lanthanum and sucroferic oxyhydroxide) which are significantly more expensive.^[11,12,13]

The most common form of phosphate binder prescribed is calcium carbonate, mainly in non-dialysis CKD. It is classically given to patients with advanced CKD and to those who are receiving dialysis^[11,14,15]. When compared to all the phosphate binders, calcium-based binders are most effective when taken with meals (which also restricts calcium absorption). They should be prescribed in combination with moderate dietary phosphate restriction, under the supervision of a certified practising dietitian^[11,12]. The foods rich in phosphate with an elevated phosphate to protein ratio (processed foods, cola drinks and fast foods) are best avoided, while foods with a high biologic value (e.g. eggs and meats) should be retained to preserve nutritional status.^[14]

In non-dialysis CKD aluminium-based binders are a second-line drug. The other newer non-calcium-based binders are

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sevelamer, sucroferric oxyhydroxide and lanthanum carbonate.^[1,13]

For all binders except lanthanum and sucroferric oxyhydroxide, depending on potency, the starting dose is typically 1–2 tablets three times daily with each meal. The dose can be increased to a maximum of six or more tablets daily for calcium-based binders and sevelamer. As phosphate binders can obstruct with the absorption of drugs such as ciprofloxacin and oral iron other medicines should be given separately.^[14]

Calcium-containing phosphate binders

In patients with CKD calcium binders are considered to be the first choice, as they also take up the hypocalcaemia that is often seen with hyperphosphataemia.^[15] They work by forming insoluble phosphate complexes in the gut. On the other hand, the main concerns with calcium-containing phosphate binders are hypercalcaemia and accelerated vascular calcification, especially when they are combined with vitamin D therapy.^[15,16] The Kidney Disease Outcomes Quality Initiative Guidelines states that in CKD doses should not exceed 1500 mg/day of elemental calcium as this produces a positive calcium balance. In spite of this little evidence of patient outcomes to support this reference. GI upset, particularly constipation is another common adverse effect of these drugs.^[16,17] The other major advantage of calcium-based binders is that they are inexpensive.^[15]

Aluminium-containing phosphate binders

Over the three decades, Aluminium hydroxide has been used for its tremendous phosphate-binding capacity. Like calcium binders they also form insoluble complexes in the gut^[12]. Due to the concerns about aluminium intoxication (dementia, osteomalacia, anaemia) a number of (principally US-based) guidelines advise against long-term use of aluminium-based binders. Some European countries as well as India still use aluminium for this purpose.^[16] If aluminium is to be used orally, regular testing of dialysis water is mandatory. In patients taking aluminium binders oral citrate must be avoided as this has been shown to lead to enhanced absorption and cases of neurological toxicity. Only a limited number of small randomised trials examining the safety and efficacy of aluminium as a binder.^[16,17]

Sevelamer hydrochloride

The most commonly prescribed non-calcium-based phosphate binder is sevelamer, but has a lower phosphate-binding capacity compared to other phosphate binders. In the GI tract these cationic polymers bind phosphates through ion exchange mechanism.^[14,17] Its off-track effects include increasing the concentrations of fetuin-A (calcification inhibitor) and lowering serum low-density lipoprotein cholesterol. These effects have not been exposed to improve cardiovascular outcome in CKD. Its main adverse effects are gastrointestinal intolerance and metabolic acidosis.^[14]

Lanthanum carbonate

The phosphate binder which has a similar affinity for phosphate as aluminium-based drugs is Lanthanum which is a trivalent metal. It is approximately twice as potent as

sevelamer and calcium.⁽⁷⁾ Lanthanum powder is more effective than chewable tablets as it reduces the pill burden. When it comes to three different tablet strengths, meaning the maximum number of tablets per day is always three.⁽⁷⁾ Lanthanum is the only oral phosphate binder used.⁽⁸⁾ Apart from poor intestinal absorption, lanthanum may deposit in tissues, predominantly bone and liver. As per studies with extended follow-up there is no evidence of bone toxicity and clinical hepatotoxicity. Similar to other phosphate binders, lanthanum may also cause GI intolerance, especially nausea. Like sevelamer, this drug is also expensive.^[9,13]

Other phosphate binders

A number of other drugs have been used as phosphate binders, including sevelamer carbonate, calcium acetate, magnesium carbonate, ferric citrate, sucroferric oxyhydroxide^[20].

Table 2: Comparison of currently available oral phosphate binders

Phosphate binder	Advantages	Disadvantages
Calcium carbonate	Aluminium free Moderately effective Moderate pill burden Cheap	Efficacy influenced by pH Unpalatable Hypercalcemia GI side effects
Calcium acetate	Aluminium free Efficacy somewhat pH dependent Moderately cheap Lower calcium load than carbonate	Large tablets have to be swallowed Hypercalcemia GI side effects
Aluminium salts	Not pH dependent Cheap	Aluminium toxicity No definite safe dose Frequent monitoring needed
Magnesium salts	Moderate pill burden Calcium and aluminium free Moderate efficacy	GI side effects Monitoring needed
Sevelamer	Calcium and Aluminium free No GI absorption Moderate efficacy Reduces total and LDL cholesterol	Expensive Efficacy influenced by pH High pill burden GI side effects
Lanthanum carbonate	Calcium and aluminium free Chewed, not swallowed whole High efficacy regardless of pH Low pill burden	Expensive GI side effects Minimal GI absorption

How effective are phosphate binders in chronic kidney disease?

In a recent Cochrane review involving 7631 participants from 60 studies, the evidence that phosphate binders reduce serum phosphate found no strong evidence for improvements in all-cause or vascular calcification, cardiovascular mortality or fracture risk.^[20]

When compared with sevelamer, calcium-based binders were associated with significantly lower serum phosphate. However, sevelamer was associated with higher risk of adverse GI events and lower risk of hypercalcaemia. There was no dissimilarity in all-cause mortality between sevelamer and calcium-based binders.^[21]

A analysis of phosphate binders reported that no phosphate binder reduced mortality compared to placebo in adults with CKD. More notably, compared to calcium –based drugs sevelamer resulted in lower mortality while the comparative effects of lanthanum and iron-based drugs were less certain.^[21,22]

Compared with calcium based binders there has not been any considerable evidence to show that sevelamer hydrochloride has reduced the cardiovascular mortality. Clinicians should not only check the level of chlorine but also the level of total of dialysis patients carbon dioxide or bicarbonate during the treatment with sevelamer hydrochloride and control metabolic acidosis.^[23]

Thus concluding, phosphate binders drastically lower urine and serum phosphorous attenuating the progression of SHPT. Among patients with CKD who have normal or near normal levels of serum phosphorous promotes the evolution of vascular calcification. The efficacy and safety of phosphate binders in CKD remain doubtful.

2. Conclusion

In patients with advanced CKD oral phosphate binders are widely used for hyperphosphataemia, even though it remains uncertain whether they improve patient outcomes such as cardiovascular events, renal bone disease and mortality. The most commonly used phosphate binder is calcium carbonate, but clinicians prescribe the more expensive, non-calcium-based phosphate binders, such as sevelamer. This is mainly due to emerging evidence that suggests calcium-based binders may accelerate cardiovascular mortality and vascular calcification. The choice of prescribing a phosphate binder will be influenced by whether or not the patient is on dialysis because non-calcium binders (sevelamer hydrochloride lanthanum carbonate and sucroferric oxyhydroxide) are not available on the PBS for non-dialysis patients. Prescription should be accompanied by patient education dietary advice, and customary review of adherence.

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