Renal Nutrition Forum
A PUBLICATION OF THE RENAL DIETITIANS DIETETIC PRACTICE GROUP
Renal Dietitians™
A DIETETIC PRACTICE GROUP OF AMERICAN DIETETIC ASSOCIATION
"Your link to nutrition and health."℠
VOLUME 23
NUMBER 3
SUMMER 2004

This issue is sponsored in part by Abbott Laboratories, Abbott Park, IL

Advances in the Treatment of Hyperphosphatemia: The Role of Lanthanum Carbonate

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Introduction

End-stage renal disease (ESRD) affects 320,000 individuals in the United States (1). Growing evidence suggests that the risk of cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD) undergoing dialysis may be related to high levels of phosphorus in the blood (hyperphosphatemia) and accumulation in body tissues (2-5). Phosphorus is a key element in a variety of cellular processes, and its deregulation in CKD can lead to serious complications.

Conventional pharmaceutical treatments have involved the use of calcium- and aluminum- based phosphorus binders, and more recently, sevelamer (Renagel®, Genzyme Corp, Cambridge, Mass), all of which work by binding dietary phosphorus in the gut, thus preventing its absorption. However, these products have certain limitations and have potential side effects. In part, this explains the finding that a significant number of patients have serum phosphorus concentrations well above acceptable levels. Since uncontrolled phosphorus levels contribute to morbidity and mortality of patients with kidney disease, there is an obvious need for new therapeutic approaches to improve the management of hyperphosphatemia, reviewed by Lowrie and associates (4). One of these new approaches is the novel calcium- and aluminum-free phosphorus binder lanthanum carbonate (Fosrenol®), currently under development by Shire Pharmaceuticals Group. Lanthanum carbonate is a highly potent phosphorus binder that acts throughout the digestive tract (even at the acidic pH of the stomach and small intestine) to bind ingested dietary phosphorus. A series of clinical studies conducted in the United States, Europe, and Asia have shown lanthanum carbonate to be safe and effective for lowering serum phosphorus levels in patients with CKD (6-8).

Hyperphosphatemia

Hyperphosphatemia is defined as a serum phosphorus level >4.5 mg/dL, usually in the form of inorganic phosphate (9). Elevated serum and total body phosphorus burdens are associated with consequences such as secondary hyperparathyroidism, calcification of vascular, cardiac valvular and soft tissues, and renal bone disease (9). The predominant cause of elevated serum phosphorus levels is the impaired renal excretion secondary to decreased glomerular filtration rate (10). An increased phosphorus load via a high-protein diet may contribute to the hyperphosphatemia, as does increased phosphorus release from bone in some patients with metabolic bone disease. Despite the fact that hyperphosphatemia is a well-known consequence of kidney failure in patients receiving dialysis therapy and is associated with poor clinical outcomes, its treatment remains elusive.

Current Therapies

The most direct method of controlling serum phosphorus accumulation is to decrease the available pool of phosphorus for absorption via the diet. Reducing protein intake and avoiding foods high in phosphorus can be beneficial. Generally, dietary control of phosphorus entails reducing intake of dairy products, dried beans and nuts and seeds, as they contribute to an average daily phosphorus intake of 1000 to 1300 mg/d (11-12). Even with dietary control and hemodialysis, phosphorus-binding agents are required to maintain serum phosphorus and total body phosphorus levels at acceptable levels (3.5-5.5mg/dl) (13).

Phosphorus binders lower serum phosphorus levels by binding ingested phosphorus and forming non-soluble complexes. These complexes cannot be absorbed and therefore are excreted in feces. The most common types of phosphorus binders are calcium, aluminum, and sevelamer (Table 1, page 4). Calcium carbonate and calcium acetate are the most common calcium-based phosphorus binders, though calcium citrate, ketovalin, and alginate are also available. The low pH of the stomach allows optimal dissociation of calcium salts and facilitates phosphorus binding (9). While they are efficacious, calcium-based binders are not ideal (14). Indeed, a major risk with the prolonged use of calcium-based phosphorus binders is the possibility of inducing a state of hypercalcemia, with subsequent elevation of the calcium x phosphorus product. The latter is strongly associated with the presence of cardiac calcification and the risk of death (15).

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Aluminum salts have been available since 1941 to treat hyperphosphatemia, the most common form used in the past being aluminum hydroxide, $Al(OH)_3$. Aluminum is a more effective binder of phosphorus than is calcium. However, aluminum salts have serious long-term side effects, including a severe form of bone disease (osteomalacia), dementia, muscle weakness, and anemia (16,17). In addition, attempts at treating aluminum deposition by chelation with desferoxamine have been largely unsuccessful (18). Therefore, aluminum salts are rarely used as chronic therapy for hyperphosphatemia in the United States.

Sevelamer hydrochloride (Renagel®, Genzyme Corp, Cambridge, Mass) is a cross-linked allyamine hydrochloride polymer (plastic) containing multiple amine groups. Protonated amines on the polymer are able to bind phosphorus groups via ion exchange. The benefits of sevelamer include good efficacy and specificity, safety, and minimal intestinal absorption (16,19). Studies have shown that sevelamer is effective in lowering serum phosphorus levels in patients on dialysis (20,21). In addition, sevelamer has secondary effects that are beneficial to dialysis patients, such as lowering of total and low-density lipoprotein cholesterol (21). Sevelamer has the disadvantage of generally needing to be administered in large amounts. This is due to the fact that sevelamer binds optimally to phosphorus at pH levels of 7.0, and phosphorus is mainly absorbed in the upper small intestine where pH levels are well below 7.0.

Another factor to consider with sevelamer treatment is its effect on concomitant vitamin D (calcitriol) therapy. Calcitriol is administered to patients with renal disease to help manage parathyroid hormone (PTH) levels. Preclinical studies suggest that sevelamer may reduce the absorption of fat-soluble vitamins, including vitamin D (22). Finally, sevelamer is significantly more expensive than calcium- or aluminum-based treatments (approximately $3000 per patient per year), and this limits access for many patients.

Lanthanum Carbonate

Lanthanum is a rare metal with an atomic weight of 139 Da. It is present in tap water and it binds phosphorus to form lanthanum phosphorus. Lanthanum carbonate is a novel non-calcium, non-aluminum phosphorus binder under development by Shire for the treatment of hyperphosphatemia. This compound acts throughout the digestive tract to bind ingested dietary phosphorus, and is a highly potent phosphorus binder, even at the acidic pH of the stomach and small intestine (23). Taken with meals, the resultant complexes are unable to be absorbed by the gastrointestinal tract (0.00003% absorption vs. 0.02% for aluminum-based compounds) (23).

A number of studies have shown that lanthanum carbonate is safe and efficacious in treating hyperphosphatemia in dialysis patients (6,7). The results of a 16-week study investigating the efficacy and tolerability of lanthanum carbonate have recently been published (6). This was a randomized, double-blind, placebo-controlled, parallel-group study. Efficacy assessments focused on the achievement of phosphorus control at levels of 5.9mg/dL, and included measurement of changes over time in serum calcium, calcium x phosphorus product (Ca x P), and PTH levels. The patients receiving lanthanum carbonate showed a rapid and pronounced decrease in serum phosphorus levels that were evident within the first week and sustained for 2.5 months. Serum levels of lanthanum carbonate were detectable at low levels, reaching an early plateau (one week), and showing no further increase during the study. There were no changes in serum calcium levels so that the significant reduction in Ca x P levels achieved during the study was entirely a result of the reduction in the serum phosphorus level. In contrast to the patients receiving calcium-based phosphorus binders, the incidence of hypercalcemia was strikingly reduced, a phenomenon universally observed in other studies comparing lanthanum carbonate with calcium-based phosphorus binders (24). Lastly and as expected, serum PTH levels were significantly lower in lanthanum car-

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Table 1. Benefits and Limitations of Common Phosphorus Binders

Binder	Benefits	Limitations
Calcium-Based (9.25,26)	• Efficient in lowering serum PO_4	• Absorbed in lower portions of the GI tract • GI upset • Risk of hypercalcemia
Aluminum-Based (9,10,25)	• Efficient in lowering serum PO_4	• Absorbed in lower portions of GI tract • GI upset • Aluminum load may cause osteodystrophy and encephalopathy
Aluminum- and Calcium-Free (sevelamer) (9,10,22)	• Not absorbed • Efficient in lowering PO_4 • Lowers low-density lipoprotein level • Serum calcium levels not altered	• Absorbed in upper portions of the GI tract • GI upset • Optimal binding at pH 7.0, requiring multiple tablet dosing • May reduce vitamin D absorption

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bonate-treated patients when compared to placebo-treated patients at the study end point. The adverse events occurring during the trial were generally limited to nausea, very similar to the events observed in the placebo population. Though lanthanum carbonate was well tolerated during this study, the long-term safety still needs to be established. Obvious toxic effects did not accompany the higher lanthanum concentrations that were noted in the serum of treated patients. However, it is not known what, if any, effect this may have over the long term.

To ensure the advantages of lanthanum carbonate over aluminum-based compounds with respect to development of bone disease, a one-year study using calcium carbonate as control was performed and followed changes in bone-biopsy profiles (7). The results were recently published and indicate no evidence of direct toxic effects on bone tissue and virtually no evolution toward low-turnover bone disease in the patients treated with lanthanum carbonate. Furthermore, patients who were previously taking calcium carbonate compounds and switched to lanthanum carbonate (for the study purposes), demonstrated a change from osteomalacic and adynamic states to more normal bone histology.

Implications for the Treatment of Patients on Dialysis

Maintaining the proper steady-state balance of total body calcium and phosphorus levels and achieving the recommended serum levels in dialysis patients continue to be a challenge. Many comorbidities in CKD patients are associated with the interplay of calcium and phosphorus absorption; changes in parathyroid function (bone metabolism); and soft tissue, cardiac, and vascular calcification. Lanthanum carbonate has the potential to become a first-line treatment for hyperphosphatemia. The drug is well tolerated, efficacious, and is not associated with a high incidence of hypercalcemia and yet is effective in reducing secondary hyperparathyroidism and lowering PTH oversecretion. Lastly, it does not affect bone metabolism, a critical toxic side effect of aluminum-based compounds.

In addition to medical nutrition therapy, it is essential for the renal dietitian to promote and develop methods to educate dialysis patients about the importance of phosphorus and calcium control. The problem of phosphorus control is compounded by the fact that none of the current binders are ideal. Patient education relevant to dietary control is essential, as well as updated knowledge about available phosphorus binders, including lanthanum carbonate.

Renagel is a registered trademark of GelTex Pharmaceuticals, Inc.

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Mark your calendars, Sunday 10/3/2004 from 1:30 to 3:00 p.m., to attend "Intensive Care to Outpatient Care: Survival Skills for Renal Practice" in Anaheim, CA. This priority session will be presented by Laura Byham-Gray PhD, RD and Karen Wiesen MS, RD, co-editors of the newly released Clinical Guide to Nutrition Care in Chronic Kidney Disease, 3rd Edition. The website www.eatright.org/Public/ConferencesAndEvents/index_18095.cfm (accessed June 22 '04) has information about 2004 ADA Food and Nutrition Conference Expo.

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