Lanthanum Carbonate: A Novel Oral Phosphate Binder

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Introduction

Hyperphosphataemia has a high prevalence in chronic renal failure and dialysis patients. In reports from dialysis cohorts 50 - 70% of patients, despite dietary advice, phosphate binders, and dialysis remain hyperphosphataemic[1]. Hyperphosphataemia is known to stimulate secretion of parathyroid hormone and suppress vitamin D3 production, thereby inducing hyperparathyroid (high-turnover) bone disease. There has been increasing interest in the observation that independently of other prognostically important factors hyperphosphataemia has been associated with excess mortality in dialysis patients [2]. Precisely how this comes about is not clear but raised plasma phosphate levels are though by many now independently to contribute to cardiovascular mortality through increased myocardial calcification and enhanced vascular calcification [3]. Hyperphosphataemia has also been associated in animal studies with cardiac microcirculatory abnormalities [4]. If these observations are correct, therefore, control of plasma phosphate is important not only for skeletal health, and normal growth, but also for prevention of the major cardiovascular endpoints that dialysis and transplant patients are prone to. Therefore, phosphate control is of prime importance. It is important to find ways to control phosphate levels early in the course of chronic renal failure in order to avoid and treat secondary hyperparathyroidism, and cardiovascular and soft tissue calcifications. However it is well-known that dietetic restrictions are often difficult to follow long term, and may come at the price of poor nutrition. Because of its large sphere of hydration and the complex kinetics of phosphate elimination, phosphate is not easily removed by dialysis. Long, slow dialysis is clearly an effective intervention for phosphate control, but this needs significant logistics and acceptance by patients - neither of which is likely to mean that by this route alone we can achieve long-term phosphate control. Thus, oral phosphate binders are now, and, we believe, will continue to be generally required to control plasma phosphate levels in dialysis patients. It is therefore concerning that none of the existing phosphate binding agents is truly satisfactory. Historically of course aluminium-containing agents are known to have the highest efficiency at phosphate binding but most clinicians have eschewed their use except for the shortest term administration because of their potential toxicity [5]. Despite the near ubiquitous use of calcium-containing agents over the last two decades, the link with recurrent episodes of hypercalcaemia and the strengthening association with their use and increased soft tissue calcifications, has started a move towards their limitation (the latest K/DOQI guidelines for example suggest calcium-salt restriction to no more than 1.5 grams of elemental calcium per day). Thus there is now a rapidly growing need for novel phosphate binders - and some of these are now available - polyallylamine hydrochloride - or at advanced stages of production prior to clinical use - magnesium-iron (metal hydroxycarbonate) mixtures, polyuronic acid derivatives and lanthanum carbonate. All of these newer drugs appear promising, and have specific advantages, but also intrinsic problems.

Lanthanum Carbonate

Lanthanum is a trivalent rare earth, discovered by Mosander in 1838. It has a use in light-bulbs and other electrical equipment. It is mined from the earth in China. In its free ionic form lanthanum is highly reactive. However it is inert in its chloride or carbonate form. Its phosphate binding capabilities have been explored for about a decade. It can provide bowel pH independent phosphate binding which can equal that of aluminium salts, and exceeds that of calcium salts. It has a low potential for systemic absorption, and very little potential for drug-drug interation [6].

Two recently published trials have examined different aspects of lanthanum carbonate as a potential phosphate binder. In the first [7], a 16-week study assessed the control of serum phosphorus with lanthanum carbonate, and its effects on serum calcium, calcium x phosphorus product, and parathyroid hormone (PTH). Haemodialysis patients greater than 18 years of age entered into a 1- to 3-week washout period during which serum phosphorus levels rose to > 5.9 mg/dL (1.90 mmol/L). In total, 126 patients were titrated with lanthanum carbonate at doses containing 375, 750, 1,500, 2,250, or 3,000 mg/d elemental lanthanum, given in divided doses with meals over a 6-week period, to achieve serum levels < 5.9 mg/dL. By the end of dose titration, 11/126 (9%) patients received > 750 mg/d of lanthanum, 25 (20%) received 1,500 mg/d, 37 (29%) received 2,250 mg/d, and 53 (42%) received 3,000 mg/d. Following titration, patients were randomized to receive either lanthanum carbonate or placebo during a 4-week, double-blind maintenance phase. At the study endpoint, the mean difference in serum phosphorus between the lanthanum carbonate and placebo treatment arms was 1.91 mg/dL (0.62 mmol/L) ($P < 0.0001$). Calcium x phosphorus product ($P < 0.0001$) and serum PTH levels ($P < 0.01$) were also significantly lower

with lanthanum carbonate versus placebo. The incidence of drug-related adverse events was similar between placebo- and lanthanum carbonate-treated patients. From this simple dose ranging study it is clear that lanthanum carbonate is an effective and well-tolerated agent for the treatment of hyperphosphatemia in patients with ESRD.

However, as lanthanum is a rare earth, there have been inevitable comparisons with aluminium. The solubility and absorption of lanthanum is orders of magnitude less than that for aluminium in man. But some is absorbed. In supratoxic doses in animals there is evidence of hepatic, and upper gastro-intestinal toxicity, but the doses used in these studies are heroic compared to clinical practice. One important study has been reported examining the effect of lanthanum carbonate compared to calcium compounds on bone histology [8].

Ninety-eight patients were randomized to lanthanum carbonate (N = 49) or calcium carbonate (N = 49). Bone biopsies were taken at baseline and after one year of treatment. Acceptable paired biopsies were available for static and dynamic histomorphometry studies in 33 lanthanum and 30 calcium patients. Blood samples were taken at regular intervals for biochemical analysis and adverse events were monitored. Lanthanum was well tolerated and serum phosphate levels were equally well controlled in both treatment groups. The incidence of hypercalcemia was lower in the lanthanum group (6% vs. 49% for calcium, $p < 0.05$). At baseline, subtypes of renal osteodystrophy were similarly distributed in both groups, with mixed bone disease being most common type. At one-year follow-up in the lanthanum group, 5 of 7 patients with baseline low bone turnover (either adynamic bone or osteomalacia), and 4 of 5 patients with baseline hyperparathyroidism, had evolved toward a normalization of their bone turnover. Only one lanthanum-treated patient evolved toward adynamic bone compared with 6 patients in the calcium group. In the lanthanum group, the number of patients having either adynamic bone, osteomalacia, or hyperpara decreased overall from 12 (36%) at baseline to 6 (18%), while in the calcium group, the number of patients with these types of bone pathology increased from 13 (43%) to 16 (53%). Lanthanum was found in bone at very small concentrations. Some lanthanum was also found in the bone of patients not taking lanthanum tablets (environmental exposure). These data show that lanthanum is a poorly absorbed, well-tolerated, and efficient phosphate binder. Lanthanum carbonate-treated dialysis patients showed almost no evolution toward low bone turnover over one year (unlike calcium carbonate treated patients), nor did they experience any aluminum-like effects on bone [8].

Conclusions

Lanthanum carbonate is a promising novel non-calcaemic, non-aluminium oral phosphate binder which is well-tolerated and effective. Its capacity for systemic absorption is low, and to date there is no evidence of an aluminium-like action on the CNS or bone. However only longer-term exposure can establish its complete safety, and it is also not clear whether it can mirror polyallylamine hydrochloride in preventing progressive cardiovascular calcifications (as polyallylamine hydrochloride also is a potent hypocholesterolaemic agent, which action may at least in part explain its success in the Treat to Goal study [9]).

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