Hyperphosphataemia and treatment with sevelamer in haemodialysis patients

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Abstract
More than 60% of patients on chronic haemodialysis (HD) have a serum phosphate level above 5.5mg/dl (1.75mmol/l), which recently has been recommended as an appropriate target in patients with end-stage renal disease (ESRD). Preventing hyperphosphataemia and elevated Ca × P product not only ameliorates the progression of secondary hyperparathyroidism and bone disease, but also appears to reduce cardiovascular morbidity and mortality from vascular calcifications. Dietary phosphate restriction and the administration of aluminium and calcium salts have been the principal means of phosphate control over the last decade. Unfortunately, the protean disturbances of toxic aluminium accumulation in the body virtually eliminated aluminium from clinical practice. Calcium-based therapy, although well tolerated, results in frequent hypercalcaemia when administered concurrently with vitamin D analogues, despite a decrease in the concentration of dialysate calcium. Sevelamer (Renagel®) has been a novel, non-absorbable calcium- and aluminium-free synthetic polymer. In initial studies, sevelamer reduced serum phosphate, Ca × P product and parathyroid hormone (PTH) in a manner comparable with calcium acetate therapy. However, the effect on PTH levels may prove to be inconsistent. It seems somewhat less effective in binding phosphate than aluminium, although no direct comparisons have been made. In a recent study, it attenuated the progression of vascular calcification in HD patients. It also binds bile acids, resulting in substantially lower low-density lipo-protein cholesterol levels. The major obstacle to its current use is a substantial increase in the cost associated with sevelamer therapy.

Keywords: calcium × phosphate product; chronic renal failure; haemodialysis; hyperphosphataemia; phosphate binders

Introduction
Preventing hyperphosphataemia and elevated calcium × phosphate (Ca × P) product, two goals of clinical nephrologists treating patients with end-stage renal disease (ESRD), is not easy to achieve. Block et al., using data from two different sets of USRDS patients who were on chronic haemodialysis (HD) for at least 1 year, reported that the mean serum phosphorus level was 6.2mg/dl. Seventy percent of these patients had serum phosphorus above normal (>5.0mg/dl or >1.6mmol/l) [1].

Controlling hyperphosphataemia improves development of secondary hyperparathyroidism and bone disease, and, more importantly, appears to reduce morbidity and mortality from cardiovascular disease, which is the leading cause of death in chronic HD patients [2]. In a retrospective cohort study of US HD patients, a phosphorus level >6.5mg/dl (2.1mmol/l) was associated with increased relative mortality risk of 1.27, and elevated Ca × P product >72mg 2/dl 2 (5.8mmol2/l2) with a relative risk of 1.34, respectively [1]. Both of these levels currently are considered unacceptable. Serum phosphorus level <5.5mg/dl (1.6mmol/l) represents standard of care as indicated in the soon to be published NKF K-DOQI guidelines; hence, this should be our goal in treating hyperphosphataemia in patients with ESRD [3].

The introduction of electron beam computerized tomography (EBCT) has improved our detection limit of relevant Ca × P product in vascular beds and heart. HD patients have 2.5- to 5-fold higher cardiac valve calcification and coronary artery calcium score when compared with the normal population [4]. This
process starts in younger HD patients, as shown in a study by Goodman et al. [5]. In this study, higher Ca×P product and intake of calcium-based phosphate binders were significantly associated with cardiac calcifications; serum phosphorus level missed a significant association (P=0.06) because of the inadequate power of the study. The mean calcification score doubled in <2 years, suggesting rapid progression during the course of HD treatment.

Conventional P binders

Aluminium hydroxide, in use since the 1960s, had the capacity to be an ideal phosphate binder. Its use has been almost eliminated because of its toxicities, including a low-turnover bone disease, dialysis dementia and erythropoietin-resistant anemia. Aluminium was replaced mostly by calcium salts in 1980s, but efficacy studies showed that calcium was less effective than aluminium in binding phosphate. The high amount of calcium that is absorbed during treatment with calcium-based phosphate binders makes hypercalcemia one of the most common complications in chronic HD patients. This becomes exaggerated in the context of calcitriol treatment, which enhances intestinal absorption of calcium and phosphorus. The incidence of hypercalcemia seems to be the same when comparing calcium carbonate with calcium acetate, despite the differences in calcium absorption [6]. More recently, serious vascular calcifications accompanying calcium loading and the increased prevalence of calciphylaxis have raised great concern about the continuing use of these agents [7]. Poor compliance with phosphate-binding therapy represents another significant limitation of conventional P binders [8].

Sevelamer (Renagel®)

Sevelamer hydrochloride was approved by the FDA for reduction of serum phosphate. It is a calcium- and aluminium-free polymer [cross-linked poly(allylamine hydrochloride)] which forms ionic, and to a lesser extent hydrogen bonds, with phosphate. Its mechanisms and effects on calcium and phosphate metabolism have been reviewed recently [9]. In a phase III crossover study spanning 8 weeks, sevelamer reduced serum phosphate and Ca×P product in a manner similar to calcium acetate (PhosLo). Hypercalcemia occurred in 5% of the sevelamer group compared with 22% in the group with calcium acetate [10]. Serum intact parathyroid hormone (iPTH) levels decreased more in patients treated with vitamin D3 than in those treated with sevelamer alone [11]. Sevelamer has been shown to attenuate the progression of vascular and aortic calcification in HD patients [12]. In this randomized clinical trial of 200 chronic HD patients, sevelamer caused less hypercalcemia, and the calcium score did not change on repeat EBCT scan in the sevelamer-treated group. Despite this impressive effect, absolute calcium scores remained in the 700 range, a level that is considered extremely high compared with the normal population. Use of sevelamer was associated with worsening acidosis. The question remains of whether this represents an important clinical consequence. Diarrhoea is another side effect, particularly in elderly patients. Long-term sevelamer treatment improves the lipid profile. Low-density lipoprotein (LDL) cholesterol decreased on average by 30% from baseline, and high-density lipoprotein (HDL) cholesterol levels increased by an average of 18% [13]. This side effect could be potentially beneficial in the ESRD population.

There is significant incremental expense in the use of sevelamer. The average cost of sevelamer is ~US$12.00 per day (US$4400/year) vs US$1.60 per day (US$585/year) for PhosLo. The addition of calcium therapy to prevent bone loss and decrease PTH will increase costs further [14]. There may be some cost savings if further studies confirm the initial data that sevelamer reduced the risk of hospitalization and the associated medical costs [15].

One strategy to prevent substantial cost increase was presented recently in a small prospective study from the UK. A regimen based on a combination of sevelamer and calcium was capable of effectively managing hyperphosphataemia without hypercalcemia at reduced financial burden [16]. The average dose of sevelamer was 2.8 g per day, which is substantially lower than the average daily dose (6.5 g) in the study of Chertow et al. [12].

Summary

An ideal phosphate binder should be non-toxic, probably calcium-free, with minimal side effects, and affordable. At this time, sevelamer is the closest to this ideal agent, but we are still awaiting the results of long-term clinical trials to convince not only traditional nephrologists but also insurance companies, state agencies and patients paying the bill that it is worth its price. It is clear that no matter which phosphate binders we use, we should aim for long-term serum phosphate of <5.5 mg/dl (<1.6 mmol/l) and Ca×P product of <55 mg2/dl2 (<4.4 mmol2/l2) [2]. Combination therapy of calcium-based phosphate binders and sevelamer may be a relatively inexpensive therapy at this time until more clinical studies with sevelamer and other new phosphate binders become available.

References

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Treatment of hyperphosphataemia with sevelamer


