Calcium-Based Phosphate Binders Are Appropriate in Chronic Renal Failure

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Many nephrologists feel threatened by the allegation that, in patients with chronic renal failure, treatment with calcium-based phosphate binders (calcium acetate and calcium carbonate) may induce coronary artery and cardiac calcification, thereby imposing a greater risk for death compared with sevelamer, a non–calcium-based binder. Acknowledging that drug manufacturers are not unaware of the marketing advantage to their product consequent to destabilizing demand for competing drugs, the case for and against abandoning calcium-based phosphate binders in favor of sevelamer is reviewed in this study. The case for continuing prescription of calcium-based phosphate binders stands on the following: (1) flawed clinical trials that favor sevelamer as a replacement; (2) weak evidence that oral calcium intake modulates vascular and/or cardiac calcification; (3) clinical trials that reinforce the safety and efficacy of calcium-based phosphate binders; and (4) the inordinate relative cost of sevelamer. Recognizing that established as well as novel phosphate binders are currently undergoing clinical evaluation, an open mind and an awareness of developing literature are necessary when deciding how to manage hyperphosphatemia in renal failure.


Distinguihing between scientific and entrepreneurial aspects that underlie an increasing proportion of current medical therapeutic controversies is challenging. Indeed, selecting an antihypertensive or lipid-lowering regimen on the basis of objective, prospective, randomized comparisons is not possible. Once sales of a single drug exceed $1 billion, market forces that back that choice are formidable, reaching out to physician-customers with festive dinners, free brief cases and pens, and multiple other rewards for receiving the advertiser’s message. Consider the accoutrements of Renal Week 2005. Our official convention bag advertised one pharmaceutical company, our registration badge hung from a ribbon celebrating another, and the CD with searchable meeting abstracts was available only by visiting the booth of a third company. Certainly, we all understand that advertising is a lubricant for capitalism and that many scientific journals carry large and attractive ads as a component of fiscal stability. Nevertheless, the need for separating being “detailed” from gaining the desired content of a “true” message is now a difficult chore.

Illustrating this contention is the reality that, of 23 “Official Symposia” authorized by the American Society of Nephrology and scheduled during Renal Week 2005, seven (30%) were sponsored by corporations that advocate a specific pharmacologic intervention for calcium-phosphorous perturbations in chronic kidney disease. Study of the handouts from these sessions suggested their origins in diverse, separate universes. Currently available and widely applied products that are prescribed to manage hyperphosphatemia in secondary hyperparathyroidism were ignored or muted during specific presentations funded by companies that champion competing drug regimens.

As an example, a conference that proposed a new treatment paradigm for managing secondary hyperparathyroidism on the basis of treatment with synthetic vitamin D included neither positive nor negative roles for cinacalcet (parathyroid cell sensor stimulant), sevelamer (phosphate binder), or lanthanum carbonate (phosphate binder). Following the lead of the US Food and Drug Administration and journal editorial boards, which struggle to weigh evidence of drug effectiveness free of investigator or sponsor bias, individual clinicians should evaluate the evidence that sustains all therapeutic recommendations underlying any specific drug purchases.

In the midst of such huckstering, nephrologists who are bewildered by the need to choose a rational phosphate-lowering regimen for individual patients have been berated for persisting in their use of calcium-based phosphate binders that allegedly induce cardiac and arterial calcification and result in greater mortality and morbidity than might have been obtained had sevelamer been the phosphate binder selected. Rallying round their 30-plus years of experience with calcium-based phosphate binders and recoiling from the five- to 10-times greater cost of sevelamer, many traditional nephrologists reject the mandate to change their drug-prescribing pattern, thereby generating a near perfect setting for the American Society of Nephrology debate conducted on November 12, 2005. What follows is a reprise of the defense of continued use of calcium-based phosphate binders in progressive renal insufficiency and during a regimen of long-term dialysis for ESRD.
Background
Depicted in Figure 1, as reported by Martinez et al. (1), are the sequential decreases in 1,25-dihydroxycholecalciferol and increases in parathyroid hormone (PTH) as a correlate of deteriorating residual estimated GFR in chronic kidney disease (CKD). Neither hyperphosphatemia nor hypocalcemia, present in 12 and 6%, respectively, of patients with CKD whose estimated GFR fell to $<30$ ml/min, is as reliable as a rise in PTH for following the course of renal function loss (2). Hyperphosphatemia, however, at levels above the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative guidelines, is a predictor (risk factor) for excess mortality. Using the large data set in the United States Renal Data System, Block et al. (3) quantified the levels of death risk for five ranges of serum phosphorous in patients who undergo hemodialysis, as shown in Figure 2. Confirmation was provided by a recent, adjusted, time-dependent survival analysis in The Netherlands: All-cause mortality risk increased in hemodialysis patients by 40% (hazard ratio 1.4; 95% confidence interval 1.1 to 1.7) and in peritoneal dialysis patients by 60% (hazard ratio 1.4; 95% confidence interval 1.1 to 2.4) for plasma phosphorous levels that were greater than the Kidney Disease Outcomes Quality Initiative target (4). An Expert Committee of the National Kidney Foundation established clinical practice guidelines for key variables in assessment of parathyroid function to preserve bone integrity in stages 4 and 5 of CKD (Table 1) (5).

Options in Management of Hyperphosphatemia
Hyperphosphatemia is a marker indicative of ongoing PTH elevation in secondary hyperparathyroidism. The therapeutic objective for correcting hyperphosphatemia is to reduce synthesis of PTH (Figure 3), a task that is accomplished by restricting dietary phosphate and binding ingested phosphate within the gut. Excess mortality in hyperphosphatemia is the consequence of injury, including calcification of the heart and arteries (especially the coronary arteries) and bone injury, previously termed renal osteodystrophy (Figure 4). Figure 5 depicts current treatment options applied to reduce PTH by lowering phosphate levels. Administration of oral calcium carbonate or acetate along with active vitamin D is the most common choice, whereas sevelamer is advocated both for its effectiveness in lowering phosphate concentration and for avoidance of the threat of toxicity attributed to calcium preparations.

Table 1. Target levels in chronic kidney disease stage 3 and 4 (2) *

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Intact PTH (pmol/L)</td>
<td>CKD stage 3 (eGFR 30 to 59 ml/min): 35 to 70</td>
</tr>
<tr>
<td></td>
<td>CKD stage 4 (eGFR 15 to 29 ml/min): 70 to 110</td>
</tr>
<tr>
<td>Serum Ca (mg/dl) corrected for serum albumin</td>
<td>8.4 to 10.2</td>
</tr>
<tr>
<td>Serum P (mg/dl)</td>
<td>2.7 to 4.6</td>
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<tr>
<td>Ca ( \times ) P product</td>
<td>(&lt;55)</td>
</tr>
<tr>
<td>Ca intake limits (mg/d)</td>
<td>(&lt;1500) from Ca-based P binders</td>
</tr>
<tr>
<td></td>
<td>(&lt;2000) from Ca-based P binders and diet</td>
</tr>
<tr>
<td>25(OH) vitamin D (nmol/L)</td>
<td>(&gt;30)</td>
</tr>
</tbody>
</table>

*Ca, calcium; CKD, chronic kidney disease; eGFR, estimated GFR; P, phosphorus; PTH, parathyroid hormone.
The Allegation

Calcium-based phosphate binders, it is charged, incur excess mortality (compared with sevelamer) by directly causing cardiac and arterial calcification. Head-to-head comparison of sevelamer and calcium-containing phosphate binders showed that the calcium-based binders induced “more rapid progression of coronary calcification than did use of sevelamer” at 6, 12, and 18 mo (6). By means of a randomized clinical trial, the Treat to Goal study, Chertow et al. (7) compared sevelamer with calcium-based phosphate binders in 200 hemodialysis patients and concluded that, compared with calcium-based phosphate binders, sevelamer caused less hypercalcemia and was less likely to be associated with progressive aortic and coronary calcification. Representative of multiple publications that have reiterated the same message, Chertow et al. (8) wrote that, although calcium-based phosphate binders led to progression of coronary artery and aortic calcification, sevelamer “attenuated or arrested progression.”

More recently, the case against calcium-based phosphate binders was reinforced by results of electron-beam tomography, which documented worsening coronary artery and aortic calcification when calcium-based phosphate binders were used but the absence of such findings in patients treated with sevelamer (9). Continuing to prescribe calcium-based phosphate binders in the face of such contrary evidence has been characterized as not only unwise but also as inappropriate medical care that adds to the morbidity and mortality of CKD patients as well as increased maintenance hemodialysis—widely followed medical practice that actually injures patients, nephrologists are warned.

Subsequently, Genzyme (Cambridge, MA), the manufacturer of sevelamer, wrote to American nephrologists on July 25, 2005, announcing results of the Dialysis Clinical Outcomes Revisited (DCOR), a 3-yr study of dialysis patients that compared sevelamer with calcium-based phosphate binders. The study’s main finding was that use of sevelamer reduced hospitalizations by 23% while decreasing mortality by 9% (10). According to the press release, Wadi N. Suki, DCOR lead investigator, termed the results, “An unprecedented moment for patients on dialysis. For the first time, a treatment has been shown to reduce the alarmingly high rate of death and illness seen in patients on dialysis.”

Refutation

On the defensive and forced to justify their continuing reliance on what is a component of standard rational renal medicine, startled nephrologists composed a composite response to the accusation that they are “killing” their patients; it consisted of arguments that are examined next.

Clinical Trials Forming the Case against Calcium Are Built on Flawed Scientific Argument

The principal clinical trial used to support the argument that sevelamer is less likely to promote calcification while significantly reducing mortality in dialysis patients is the Treat to Goal study. Standard criteria of statistical design were not followed in the protocol (11). Examples of limitations are that the study was not blinded, vitamin D therapy was significantly followed in the protocol (11). Among other rejections of the “anti-calcium” view, Fournier et al. (13) afforded excellent perspective. Noting that vitamin D supplements were given to study participants, Fournier et al. reasoned that, as a result, PTH levels may have fallen below target range in the calcium group. PTH oversuppression may have led to less bone turnover, less dense bone, and reduced capacity for supplemental calcium to enter bone, resulting in a higher risk for hypercalcemia and associated soft tissue calcification (14). Other flaws in the Treat to Goal trial include failure to control for variables that could affect the rate of cardiovascular calcification, including dialysate calcium, vitamin D dose, and lipid levels (15). Qunibi (16) speculated that sevelamer may have been responsible for a reduced rate of vascular calcification as
a result of its LDL-lowering effect because the drug is “a known anion exchange resin and a bile acid sequestrant that lowers serum levels of LDL by 20% to 30%” (17).

The most recent sevelamer versus calcium-based phosphate binder trial—the DCOR trial—has not been published but was presented during Renal Week 2005. In an open-labeled, multicenter, parallel design study of 2103 hemodialysis patients randomly assigned to receive sevelamer or a calcium-based phosphate binder, a 9% reduction in all-cause mortality was attributed to the use of sevelamer (9). Until editorial review is completed, one reservation to accepting the significance of mortality reduction as conclusive is that DCOR did not include the prospectively defined primary end point or any prospectively defined secondary end points. It will be a chore for statisticians to decipher whether it is legitimate to restate an end point after the fact, although recollection of the author’s course in elementary medical statistics suggests that it is not.

Literature Does Not Substantiate Calcium Critics’ Allegations

Neither cardiac nor arterial calcification is a newly recognized complication linked to use of calcium-based phosphate binders. Illustrating this contention is the report of the anatomic features of a 5300-yr-old mummy, named “the iceman,” which was found frozen in the Tyrolean Alps (18). A total of 38 radiographic and approximately 2190 computed tomography images permitted extensive inferences of life events in the corpse, who was estimated to have died at the age of 40 to 50 yr. Pertinent to this discussion is a transverse computed tomography section of the iceman’s lower abdomen, demonstrating extensive linear calcification of the aorta, cens before the first calcium-based phosphate binder became available.

Negative studies that pertain to the value of sevelamer were omitted from discussion in the case presented by sevelamer proponents. For example, a prospective study of calcium carbonate (4.8 g/d) versus sevelamer (2.4 increased to 4.4 g/d) as a phosphate binder was conducted in 42 French hemodialysis patients (19). Each month, when serum calcium values were assessed, a calcium concentration <2.3 mmol/L was treated by either increasing dialysate calcium level or by adding treatment with α-calcidiol at each dialysis, as guided by serum phosphate levels. The only differences discerned between the two groups were that the sevelamer group had a higher serum phosphate, a lower bicarbonate, and lower LDL cholesterol. PTH control was equivalent in both binders.

Further undermining any strong association between oral calcium intake and the extent of vascular calcification is a trial by the Institut National de la Santé et de la Recherche Médicale Electronic Resources Inventory Group—Amiens Medical School and Jules Verne University (http://www.omerad.org/cgea). Presented at the 2005 convention of the European Dialysis and Transplant Association but not yet published, this study was a long-term observational clinical trial that sought to discern a causal relationship between oral calcium dose and all-cause mortality and vascular calcifications in hemodialysis patients (20). Patients were followed from January 1, 2000, until December 31, 2003, or end points of death or a cardiovascular event. Of 57 patients (37 men and 20 women) who were enrolled in the study, 47 had aortic calcifications. Dialysis was performed using a 1.5-mmol dialysate; calcium and phosphate binding were effected with oral CaCO₃ supplements (daily dose of 6 to 9 g; i.e., 2.4 to 3.6 g/d elemental calcium). Each patient had an entry radiograph of the lumbar spine as well as measurement of bone mineral density. Leptin, osteoprotegerin, and other nutritional, hormonal, and inflammatory parameters were monitored. Main findings, using the Framingham Calcification Score, were that there were no links between aortic or iliac calcification and oral calcium load, hyperphosphatemia, hypercalcemia, hyperbicarbonatemia, or either PTH level or low bone turnover. The extent of aortic calcifications and the level of bone density were not linked. The only correlates of all-cause mortality were the extent of vascular calcification and patient age.

Consensus of Users Finds Calcium Is Not Linked to Cardiac or Vascular Complications

Which variables are actual risk factors for cardiac and/or vascular calcification in renal insufficiency? To address this question, McCoullough et al. (21) reviewed Medline citations (65,474 vascular, 74,198 blood vessel, 26,933 calcium, and 3742 phosphorous) with abstracts in English on humans and adults as of August 11, 2002. Thirty studies met predetermined criteria that permitted inferences of association between cardiac and vascular calcification and major purported risk factors: 11 prospective cohort, seven cross-sectional, 11 case control, and one retrospective cohort study.

The striking finding of McCoullough’s literature analysis is that only three of 30 studies implied any independent association between oral calcium load and cardiac and/or vascular calcifications. The main determinants of cardiac and vascular calcification discerned were patient age, duration of dialysis treatment, and, inconclusively, dyslipidemia. In another fascinating but pertinent study, the only evaluation of the prognostic significance of coronary calcifications in hemodialysis patients who were subjected to coronary dilation concluded that coronary calcification predicted a favorable outcome rather than the reverse (22).

Expense of Sevelamer Excludes Its Use by Many (Most?) Patients with CKD

Although there are differences by gender, age, and race, the overall annual Medicare cost per patient to deliver maintenance hemodialysis is approximately $68,000 (23). Understandably, with federal budget deficit increases, awareness, converted to consternation, has intensified along with attention to the fiscal consequences of the ESRD program that now consumes approximately $18 billion annually. After adjustment to the billions of dollars for the cost of erythropoietin as a dialysis regimen component, focused resistance to incorporation of another $1-billion drug for phosphate binding must be addressed. The arithmetic is straightforward. The relative cost per year of currently approved phosphate binders, as listed by a Veterans Administration expert advisory committee (24), ranges from
$46 to $145 for calcium acetate, to $1200 to $2400 for lanthanum carbonate, and $360 to $2824 for sevelamer. State and private insurer approval of prescriptions for sevelamer varies widely, as does the price charged by drug manufacturers to each agency. From generalized personal observations and inquiries, however, I conclude that sevelamer is viewed by many patients who contribute to their drug purchases as too expensive for routine use given the current evidence to sustain claims of its unique efficacy. Clearly, the quality of response to the plea for stronger evidence on behalf of sevelamer will guide the extent of its subsequent use.

**Predicting the Next Step in the Phosphate Binder Saga**

Complicating assignment of a specific place for sevelamer in the quest for optimized phosphate binding is the recent Food and Drug Administration approval of lanthanum carbonate as a phosphate binder for dialysis patients. About as costly as sevelamer (24), benefits attributed to lanthanum include a lower incidence of hypercalcemia (2.7%) compared with calcium-based phosphate binders (20.2%) and maintenance of the calcium × phosphate product at an acceptable level with only mild to moderate adverse effects (25). A serious caution to the uniform adoption of lanthanum has been raised, however, because, like aluminum, which ultimately was discontinued because of bone and neurologic toxicity, lanthanum is a rare earth metal. Lanthanum ions are absorbed, although to a minimal extent, in the human gut, whereas its blood concentration is increased 10-fold and bone concentration five-fold after short-term supplementation in patients with CKD (26). Initial pricing of lanthanum carbonate approximates that of sevelamer at nearly 10 times that of calcium acetate and/or carbonate phosphate binders, foreshadowing yet another market combat between dueling pharmaceutical firms.

Seeking perspective 2 weeks after the debate during Renal Week 2005 over risking heart and arterial calcification when binding phosphate, as this is written, there is concern that the sometimes heated argument might have been a futile exercise in sound and fury to no productive end. However, if only a few colleagues newly realize that they are players in an intense drama that will affect their decision as to how to treat hyperphosphatemia in CKD, it will have been worthwhile. Admittedly, unequivocal proof of a worrisome risk surrounding use of calcium-based phosphate binders may materialize from studies that have not been conducted and/or reported yet. By contrast, sevelamer conceivably could emerge from the current arena of charge and countercharge confusion as the only safe option, delivered at a restructure-pricing scheme that imposes less of a budget-breaking threat. Until this debates is resolved, the guidelines in Table 2 should be followed.

In the winter of 2005 to 2006, however, there is no reason to panic over unsuspected or unrealized damage to our patients with CKD that might be induced by calcium-based phosphate binders. Instead, note the position of the American Society of Nephrology, stipulated by Goldberg in the Nephrology Self-Assessment Program (NephSAP) issue for March 2004: “While there is some evidence implicating calcium-containing phosphate binders in the progression of vascular and cardiac calcification in patients receiving chronic hemodialysis, the hypothesis that the calcium-containing binders are the root cause of vascular and cardiac calcification remains largely unproven. As calcium acetate is more cost-effective than sevelamer and is effective in controlling serum phosphate, it remains an accepted first-line drug” (27). During the summer of 2005, there were intense, cross-company accusations of spurious, fatally flawed analyses of ongoing trials of sevelamer versus calcium-based phosphate binders. NephSAP reexamined the issue in September 2005, this time with the instruction that “conclusions regarding the relative merits of sevelamer compared with calcium acetate or calcium carbonate, or other lipid-lowering strategies, remain controversial and await confirmation by better-controlled and longer-term studies” (28). This author concurs fully.

**References**

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