

Phosphate Binders: Hold the Calcium?

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Several retrospective studies of large databases have shown that most dialysis patients have elevated levels of serum phosphorus and that this elevation, independent of a variety of relevant variables, adversely affects patient survival (1,2). Although there are no data demonstrating that a reduction of serum phosphorus will improve survival, a prudent clinician cannot dismiss this compelling epidemiologic evidence and will strive to lower serum phosphorus in dialysis patients. Although the Kidney Disease Outcomes Quality Initiative guidelines indicate that a serum phosphorus value that exceeds the upper limit of normal is acceptable for dialysis patients (3), more recent data suggest that we should aim for a level of phosphorus within the normal laboratory range (4).

Phosphorus is ubiquitous in our daily diet, and its absorption is poorly regulated. We continue to absorb approximately 60 to 70% of dietary phosphorus regardless of bodily needs or renal function (5). As our renal excretory capacity diminishes, unrelenting absorption coupled with impaired excretion results in phosphorus retention. Dialysis effectively removes a single day's worth of absorbed phosphorus (6); our patients generally receive dialysis only 3 d/wk, but they continue to eat on all 7 days. Therefore, to prevent phosphorus retention, we must first decrease dietary phosphorus, which results in less absorption and is always worthwhile but limited by the necessity to provide simultaneously adequate protein; second, inhibit intestinal phosphorus transport, which, although promising, has not reached the clinical arena; third, prescribe more frequent dialysis, which effectively prevents phosphorus retention but is not yet practicable for the majority of patients; and/or fourth, lessen absorption by binding intestinal phosphorus, which leads to increased fecal excretion, an approach used in the vast majority of dialysis patients.

How, then, should we bind intestinal phosphorus in dialysis patients? The ideal agent should selectively and irreversibly bind large amounts of phosphorus, require only a few relatively small pills, have no absorption or toxicity, and be inexpensive. None of the currently marketed phosphorus binders entirely satisfies these parameters. Because of toxicity, we have effectively eliminated aluminum as a binder. We are left with calcium-containing agents—calcium carbonate and calcium acetate—and non-calcium-containing agents—sevelamer hydro-

chloride and lanthanum carbonate—and others such as iron and magnesium that are infrequently used.

The current controversy revolves not around the need to bind phosphorus, for which there is broad agreement, but around the contribution of elemental calcium in calcium-containing phosphorus binders, if any, to vascular calcification and death. Moe and Chertow (7) argue that phosphorus is a uremic toxin; that serum calcium levels do not reflect calcium balance; that vascular calcification is a cell-mediated process accelerated by hyperphosphatemia and excess calcium load; and that in prospective, randomized studies, calcium-based phosphorus binders lead to increased arterial calcification, whereas the non-calcium-based phosphate binder sevelamer does not. Friedman (8) argues that the clinical trials that favor sevelamer are flawed, that the evidence that oral calcium intake modulates vascular and/or cardiac calcification is weak, that clinical trials reinforce the safety and the efficacy of the calcium-based phosphate binders, and that sevelamer is inordinately expensive.

In adult, nonpregnant humans, if net calcium absorption exceeds urine calcium excretion, then calcium must be retained (5). Dialysis patients absorb approximately 20% of dietary calcium, which increases with exogenously administered vitamin D₃, and have essentially no urine calcium excretion, although there are small extrarenal losses (9). If the dialysis treatment itself results in no net calcium flux, then any absorbed calcium must be retained. Once bone calcium stores are replete, excess calcium must accumulate, with phosphorus as the preferred anion, in extrasosseous sites with potential detrimental consequences. Indeed, repeated studies have shown excess calcium deposition in dialysis patients (10,11). Elevated serum phosphorus, which has the potential to transform vascular smooth muscle cells into collagen-secreting osteoblasts (12) and to bond with normal or perhaps elevated serum calcium, leads invariably to an elevated calcium × phosphorus product. The elevated product increases supersaturation for calcium phosphorus solid phases, potentially overwhelming inhibitors of calcification (13,14) and leading to deposition of calcium and phosphorus on this extrasosseous, collagen matrix. Once the initial solid phase is formed, thermodynamics favor rapid crystal growth. This analysis argues against addition of oral calcium, especially when given with vitamin D₃, the principal hormonal regulator of calcium and phosphorus absorption (5).

One should always support hypothetical arguments with facts. Two carefully performed, randomized, prospective studies demonstrated that use of the non-calcium-containing phosphate binder sevelamer attenuated progression of vascular cal-

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cification compared with calcium-based phosphate binders (15,16). Neither study was powered to demonstrate differences in mortality nor immune to thoughtful critique; however, the converse, that calcium-containing phosphate binders retard the progression of calcification compared with non-calcium-containing binders, has yet to be presented.

What, then, prevents nephrologists from using sevelamer or, perhaps, the other non-calcium-containing phosphate binder, lanthanum, exclusively? The negatives for sevelamer are the risk for acidosis and the large pill burden, the negative for lanthanum is the risk that retained lanthanum will be toxic, and the negative for both is the cost. Bicarbonate concentrations are slightly but significantly lower with sevelamer-treated patients (15), and lanthanum accumulates in uremic rat bone and liver (17,18), although there has been no adverse effect on patient outcomes. Lower cost remains a compelling force for using the calcium-containing phosphate binders (8).

In patients with chronic kidney disease, an important therapeutic goal should be normalization of serum phosphorus, and it probably is better to lower phosphorus using whichever binder the patient can afford. However, if cost can be tolerated or mitigated through insurance or other programs, then the use of a non-calcium-containing binder, especially sevelamer as it was used in the prospective studies (15,16), seems preferable. Although some have argued that the costs to society should limit the use of potentially beneficial mediations, few missions should be more important to a nation than the health of its less fortunate citizens. Physicians take an oath to provide optimal care to patients, not to help balance budgets.

Physicians must act, before they have the benefit of the well-designed clinical studies that show a reduction in mortality, in ways they reasonably determine is in their patients' best interests. The adage is to "first, do no harm;" in this case, normalizing serum phosphorus in dialysis patients without adding calcium seems most prudent.

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