Should we consider the cost-effectiveness of the different therapies when applying the recommendations on phosphorus-chelating agents?

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The nephrologist managing patients with CRF, especially those on dialysis, are frequently faced with taking a decision on the prescription of phosphorus-chelating agents; and this is a complex decision. All medications that are currently used as phosphorus-chelating agents (aluminum hydroxide, calcium acetate and calcium carbonate, magnesium salts, sevelamer, and lanthanum carbonate) are effective decreasing serum phosphate levels, although there are not enough comparative data on their efficacy to recommend the use of a particular chelating agent in every patient. Besides, the number of tablets added to the patient's regimen is high and the costs very different. It is true that the epidemiological data show a positive association, although not a causal relationship, between high serum phosphate levels and morbimortality; however, the benefits derived from decreasing serum phosphate levels on the patients' clinical course (hospital admission, fractures, cardiovascular events, or mortality) have not been studied so far.

The present study aims at exposing the information available on the issue and making the nephrologist aware of the fact that just by prescribing to a patient one phosphorus-chelating agent he/she might be increasing the health care expenditure by some additional 2500 euros/patient/year.

SOME CONSIDERATIONS ON CURRENT PHOSPHORUS-CHELATIN AGENTS

Aluminum hydroxide

At the beginning of the 1970s the use of aluminum-containing phosphorus-chelating agents was the first-choice method since non-absorbable products were created within the intestinal lumen. Aluminum hydroxide was a very effective phosphorus-chelating agent[1] but unfortunately its long-term use was associated to aluminum accumulation and toxicity, which manifests as encephalopathy, osteomalacia, microcytic anemia, and myopathy.[2-4] The result is that the use of aluminum hydroxide has been limited to emergency treatment and short-term therapy, and finally has been definitively abandoned.

However, all the complications related with aluminum deposition in the CRF patient were motivated by very high content of aluminum in the water before the systematic use of inverse osmotic processes generating quality water for hemodialysis. There are publications, especially in children, about the use of aluminum hydroxide p.o. and its repercussion on the organism. Its very poor intestinal absorption (0.01%) is compensated by a 90% renal clearance. It has the advantage of the cumulated experience showing that it is a powerful and highly effective agent. There are no prospective randomized studies showing the toxicity of aluminum at appropriate doses, taken with food and not on an empty stomach, in patients managed with water with aluminum concentrations lower than 5 mg/L. The eventual toxicity is long-term toxicity and the cost is very low (which may be the cause for abandoning this drug lacking a commercial sponsor).

We may therefore summarize at the present time that aluminum hydroxide is an excellent chelating agent that might be contraindicated for very long periods of time and in those cases of adynamic bone disease. By contrast, it would not be absolutely contraindicated for short periods, in advanced-age patients (with short life expectancy), and in patients with a high likelihood of being transplanted. It should be administered with a full stomach because its absorption in an acid milieu is higher.

CALCIUM-CONTAINING AGENTS

Calcium carbonate

Calcium salts have been an important alternative as phosphorus-chelating agents to replace aluminum. Calcium carbonate better dissolves in an acid milieu and its binding to phosphorus improves with high pH and significantly decreases when pH goes below 5, so that it is less effective than aluminum. Calcium carbonate controls phosphorus adequately, although its effectiveness is limited by the possibility of hypercalcaemia. Calcium carbonate contains a high proportion of elemental calcium (40%) and hypercalcaemia occurs when it is administered at high doses, or concomitantly with vitamin D (which increases calcium intestinal absorption), or with the

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use of high calcium concentrations in the dialysis bath (> 2.5 mEq/L). As we have previously mentioned, the proportion of calcium absorbed dramatically increases when it is not synchronized with the meals, and higher amounts of elemental calcium are absorbed when calcium carbonate is given on an empty stomach or two hours after the meals, as compared with its administration immediately after the meals.[5]

Calcium acetate

This is an alternative to calcium carbonate as a phosphorus-chelating agent and, in addition, its content in elemental calcium is lower (25%) than with calcium carbonate. This translates into the fact that the amount of phosphorus bound per amount of calcium absorbed is twice as high with calcium acetate than with calcium carbonate. In a study, Mai et al. showed that phosphorus absorption decreased to 40% of that ingested with calcium acetate as compared with 21.7% with an equivalent amount of calcium carbonate; that is to say, in patients with advanced chronic renal disease calcium acetate binds approximately twice as much phosphorus per amount of calcium absorbed.[6-8] This explains why calcium acetate has better solubility in both acid and alkaline solutions. However, this effect that just half the amount of calcium is required with calcium acetate for the same chelating effect should not overlook the possibility for hypercalcaemia with high doses of calcium acetate.

Dosage of calcium-containing agents

The dosage of calcium-containing phosphorus-chelating agents is generally increased until the serum phosphate level ranges 4.5-5.5 mg/dL or hypercalcaemia occurs since plasma calcium levels should be kept at the low normality range (8.4-9.5 mg/dL) and the calcium-phosphorus product < 55 mg/mm^2. Given the eventual complication of occurrence of coronary artery calcifications with calcium-containing compounds[9] the working group of the K/DOQI guidelines suggests that the total amount of elemental calcium (including that contained in foods) should not exceed 2,000 mg/day, so that the amount of elemental calcium administered should not exceed 1,500 mg/day. This means that the maximal dose of calcium acetate is 6 grams, and for calcium carbonate 4 grams. Even this calcium dosage produces a positive calcium balance if the patient is receiving vitamin D, which may have long-term consequences. Besides, the K/DOQI guidelines recommend that calcium-containing phosphorus-chelating agents should not be used in hypercalcaemic dialysis patients (corrected serum calcium > 10 mg/dL) or in those with parathyroid hormone levels < 150 pg/mL).

Controversies about the indication of calcium products in patients with chronic renal disease

There exist many controversies about the use of calcium-containing phosphorus-chelating agents. It is a complex matter to analyze the reason for these controversies although there exist unquestionable and very reasonable facts warranting the use of calcium salts as phosphorus-chelating agents,[10] as well as others advising against it,[11] although we have to assume that there exist an important commercial pressure on this issue. Among the reasons why Friedman[10] recommends the use of these calcium compounds in chronic renal disease is that there are no clear-cut clinical trials warranting the replacement of these agents by Sevelamer in particular, which is the calcium-free product currently available on the market. Besides, Friedman states that there is very weak evidence that oral intake of calcium modulates vascular or heart calcification, that the clinical trials supporting the safety and efficacy of calcium-containing phosphorus-chelating agents are numerous, and finally he points out the extraordinary cost of sevelamer. Also considering that these new calcium-free phosphorus-chelating agents are currently under clinical evaluation, in his opinion, it is necessary to clearly and with an open mind think about what we really know from the literature and in how many clinical trials are designed to meet the interests of a particular trade.

On the other hand, Moe[11] states that there is sufficient evidence from prospective randomized trials showing that the use of calcium-based phosphorus-chelating agents contributes to progressive coronary heart disease and aortic calcification as compared with calcium-free products such as Sevelamer. In his opinion, there is biological evidence that hyperphosphatemia and exogenous calcium administration may accelerate vascular calcification. Unfortunately, there is no bedside test that can determine what may be the amount of calcium salts, either as maintenance therapy or as cumulative doses that may be safely administered, and unfortunately, the serum calcium level does not reflect the calcium balance. His opinion is that calcium-chelating agents should be restrained in many, if not all, patients on dialysis.

In my opinion, calcium compounds used at a dosage not higher than 1,500 mg/day of elemental calcium (we have already mentioned that each gram of calcium carbonate has 40% of elemental Ca and calcium acetate 25% of elemental Ca) are effective products, provided that serum calcium levels are kept under the recommended values of 10 mg/dL, and particularly cheap; thus, for me there is no reason to advise against them in the benefit of other drugs considerably more expensive. I consider reasonable to avoid prescribing them in those cases with low bone turnover and PTH levels below the normal range for these patients, according to the method used (< 100 pg/mL). The calcium concentration in the dialysis fluid should be reduced to 2.5 mEq/L, allowing so maintaining a safe calcium intake while preserving the chelating effect and avoiding excessive calcium gain.

Sevelamer

Sevelamer is a non-absorbable polymer that does not contain calcium or aluminum and that binds phosphate through ionic exchange. The product is resistant to digestive digestion and

binds dietary phosphate by releasing chloride.[12] In addition, it also binds biliary acids and decreases LDL-cholesterol.[13]

There are many studies assessing the efficacy of sevelamer in decreasing serum phosphate levels,[12-22] and although all of them found out that sevelamer was effective, there are publications discussing its relative efficacy when compared to other phosphorus-chelating agents. There is a prospective study called «Treat to Goal» on 200 hemodialysis patients receiving sevelamer or calcium compounds.[19] This study showed how within one year of therapy serum phosphate levels were similar with both agents (5.1 mg/dL). However, sevelamer had some associated beneficial effects such as lower incidence of hypercalcemia (5% *versus* 16%), a minimal decrease in serum calcium level (9.5 *versus* 9.7 mg/dL), lower incidence of low PTH levels (30% *versus* 57%), lower LDL-cholesterol (65 *versus* 103 mg/dL), and a very much lower percentage in the mean absolute score of calcium within the coronary arteries (5% *versus* 25%) and the aorta (5% *versus* 28%). Besides, further studies also showed that sevelamer led to decreased C reactive protein values.[23] This Treat to Goal study has been criticized because the number of patients withdrawing from the study was high, it was not blind, and the patients received different calcium concentrations in the dialysis bath.

In another study called CARE (Calcium Acetate Renal Evaluation) the authors found out that calcium acetate achieved better control of phosphorus and phosphate-calcium product than sevelamer,[24] although calcium levels were higher. This is a short-term study already pointing out calcium acetate as a cost-effective drug in the first line therapy for controlling phosphate-calcium metabolism.

There are other studies relating the effect on mortality of sevelamer. The DCOR study assessed the mortality among 2,103 HD patients receiving sevelamer or calcium-containing phosphorus-chelating agents. At 45 months no differences were found in mortality causes.[25]

An issue to be considered with sevelamer is that it induces metabolic acidosis so that it should not be used in patients that are not on dialysis. It is a product offering hydrogen ions (sevelamer HCl). A variant with carbonate will be available in the future to avoid this problem.

Systematic review on the clinical efficacy and safety of Sevelamer in dialysis patients

A study has recently been published bringing together the different publications that compare sevelamer with other types of therapies or with placebo in dialysis patients.[26] The authors identified 14 publications of randomized studies (3,193 participants) that were eligible for the efficacy analysis. They found that in the 10 studies reporting phosphorus and calcium levels (2,501 participants), serum phosphorus was significantly lower with calcium-chelating agents by 0.12 mmol/L (95% confidence interval) as compared with sevelamer. The phosphate-calcium product was not significantly different in patients receiving calcium compounds as compared with sevelamer. The mean difference in serum calcium was significantly lower with sevelamer (0.10 mmol/L) and bicarbonate was significantly lower in those patients receiving sevelamer, with 2.8 mmol/L. In the 5 studies reporting all mortality causes (2,429 patients) the risk differences for all mortality causes were similar between the different therapies. In the 3 studies reporting serious adverse events, there was a trend towards a lower risk in those patients receiving calcium-chelating agents. The authors conclude that, when compared to calcium-containing chelating agents, the use of sevelamer in dialysis patients is associated with similar or slightly higher serum phosphate levels, similar phosphate-calcium product, and slightly lower serum calcium levels. There is no evidence showing that sevelamer reduces all mortality causes, cardiovascular mortality, the frequency of symptomatic bone disease, or the patients' quality of life.[27]

In the same issue of the journal there is an editorial («*Sevelamer a Promising and unproven drug*»)[27] in which it is recognized that sevelamer has a potential advantage over calcium-based compounds regarding the improvement in vascular calcification. However, the inference of the specific effects of this drug on better survival in patients with chronic renal disease has not been shown so far.

Lanthanum carbonate

Lanthanum carbonate (LC) belongs to a group known as «lanthanides» and has low solubility. In the acid milieu of the stomach and within the proximal intestinal region, LC sufficiently dissociates to chelate phosphorus. In experimental and comparative studies it has been shown that LC is as effective as aluminum hydroxide and more effective than calcium carbonate or sevelamer.[28]

There are different studies with lanthanum carbonate showing that it is effective and well tolerated in healthy volunteers and also in HD patients.[29-33] However, therapy with lanthanum carbonate at doses between 1500 and 3000 mg/day could not decrease sodium phosphate below 5.5 mg/dL in many of these studies.

One of the problems with LC is long-term safety, particularly its effects on the bone and other organs are unclear.[34-35] 100-fold higher LC levels were found in the liver of uremic rats taking LC as compared with rats receiving a control diet, although there seemed not to be signs of liver toxicity at the end of 4 years of therapy.[36]

The general impression is that the use of lanthanum carbonate will be similar to that of sevelamer taking into account its high cost. It may be used in patients with hypercalcaemia, in those with PTH below normal levels, or as a complementary therapy to 1,500 mg of calcium-containing phosphorus-chelating agents if phosphorus levels are above 5.5 mg/dL. It has the advantages of being a more potent phosphorus chelator, its price will likely be high although lower than sevelamer, and the number of tablets will be 3/day instead of 8/day with sevelamer in order to yield 6.4 g/day.

REASONS FOR THERAPY FAILURE WITH PHOSPHORUS-CHELATING AGENTS

These reasons may be observed in Table 1 that shows that most of them relate with a lack of adherence or incorrect dosage with the meals.

Table I. Reasons for therapy failure with phosphorus-chelating agents

- *Lack of adherence*
  - The chelating agent is not taken at the indicated time: in the middle of each meal.
  - Negligence of adherence.
  - Less than the prescribed medication is taken.
- *Fixed regimens of drug intake (and prescription)*
  - E.g: «two tablets at each meal», without taking into account the daily variations of meals (it has been observed that the differences in phosphorus intake between the breakfast, lunch, and dinner may vary from 100 to 800 mg).
  - Eating during dialysis without taking into account that it should be accompanied by phosphorus-chelating agents, which in many instances are not administered (it may account for 400 mg).
  - Most of the meals are not accompanied by the adequate dose of phosphorus-chelating agents (it has been calculated to be of only 30%).

WHAT SOULD WE CONSIDER WHEN PRESCRIBING PHOSPHORUS-CHELATING AGENTS?

The answer is easy: efficacy and safety, cost-benefit, and number of tablets needed. An «automatic» prescription derived from the influence of pharmaceuticals based on some relevant scientific article (although without a strong evidence as we have seen) may unacceptably increase the cost in relation to the benefit obtained.

Besides, adherence to therapeutic prescriptions of phosphorus-chelating agents is rather low. We should take into account that dialysis patients receive prescriptions for multiple medications and we know that treatment adherence does not reach 50% in chronic diseases. Many times, in many patients the use of these drugs is associated with gastrointestinal problems and the excessive number of pills leads to lack of adherence, loss of appetite and its nutritional consequences, and lack of quality of life.

In a study that we performed among several dialysis units in Spain aimed at describing the characteristics of mineral metabolism impairments, we also carried out a financial analysis to document the treatment cost and determine whether or not this was associated to the mineral status. We studied 1,312 patients of whom 51% received calcium-chelators, 21% sevelamer (currently this figure reaches 49% in a sample of the ANSWER study on 2,500 incident dialysis patients within one year), 16% aluminum hydroxide, and 29% did not receive chelating-agents. Thirty-three percent of the patients received calcitriol. In this group of patients from these Spanish units, the prevalence of patients not meeting the KDOQI goals were 50% for calcium, 46% for phosphorus (in the Answer study with 49% of the patients receiving sevelamer, 44% had serum phosphorus higher than 5.5 mg/dL), 33% for the calcium-phosphorus product, and 77% for PTH. Those patients worse controlled were also those accounting for higher additional costs related with phosphorus control.[37]

The products more commonly used available in the Spanish market are:

1. *Aluminum hydroxide,* 233 mg tablets, container with 50 tablets, price 1.18 euros, mean number of tablets needed 6. Total daily cost 0.141 euros.
2. *Calcium acetate,* 500 mg capsules (125 mg of elemental calcium), container with 120 capsules, price 12.04 euros, mean number of tablets needed 6, Total daily cost 0.6 euros.
3. *Calcium carbonate,* 1,250 mg tablets (500 mg of elemental Ca), container with 90 tablets, price 5.01 euros, mean number of tablets needed 3, total daily cost 0.167 euros.
4. *Sevelamer,* 800 mg tablets, container with 180 tablets, price 157.03 euros, mean number of tablets needed 8, total daily cost 7 euros.
5. *Lanthanum carbonate,* not commercially available in Spain at the present time, 750 mg tablets, container with 90 tablets, price 181.48 euros, Mean number of tablets recommended 3, total daily cost 6 euros.

Considering the number of tablets (an average calculation is done based on the prescription frequency and the technical specifications) per month and year, and the prices for the year 2007, and assuming that the patients had perfect treatment adherence (it is never so, and some estimate an 80% of adherence rate, which is also excessive), the decision on prescribing one chelating-agent or the other implies:

Medication	Num. of tablets/day	Cost/€ month	Cost/€ year
AL OH	6	4.28	51
Calcium carbonate	3	5.07	61
Calcium acetate	6	18	219
Sevelamer	8	209	2,512
Lanthanum carbonate	3	181	2,178

There is a very interesting economical study by Manns *et al.*[38] comparing the use of sevelamer and calcium carbonate in a simulated cohort of American dialysis patients analyzing costs and survival. The conclusion does not favor the use of sevelamer.

The nephrologist should know that prescribing an aluminum- or calcium-free product for controlling hyperphosphatemia in dialysis (sevelamer at the time of writing these lines) may suppose increasing the costs by 209 euros per month, on average. Considering that each year 5,000 patients start on dialysis, of which 50% have a phosphorus level > 5.5 mg/dL, the cost just for these incident uncontrolled patients would be higher than € 6 million per year had they been treated with calcium-free chelating agents. Let us remember that the num-

ber of prevalent dialysis patients is about 23.000. Taking all this information together, and applying information we have available, the invoicing of the only aluminum- and calcium-free phosphorus-chelating product available in our country is about € 20 million per year. And this expenditure seems not to be related with a decreased hospitalization rate, cardiovascular events, or morbimortality.

THE AUTHOR'S RECOMMENDATIONS ON PRESCRIPTION OF PHOSPHORUS-CHELATING AGENTS (P > 5.5 MG/DL)

The first measure after reviewing the diet and the dialysis efficacy is to reduce or withdraw the therapy with vitamin D or analogues in those patients receiving them. After two-three months, always consider repeating phosphorus measurement when P > 5.5 mg/dL (it is the trend and not an isolated value which should prone us to change prescription).

PTH < 100

– Sevelamer (except in patients not on dialysis) or lanthanum carbonate.

PTH > 100

– *Serum calcium level < 10 mg/dL:*
  1. Calcium acetate or calcium carbonate
  2. Associate aluminum hydroxide (if Ca > 10 mg/dL or serum P persists > 5.5 mg/dL) during a period of time that depends on P control and the patient's characteristics.
  3. If there is no control, associate lanthanum carbonate (3 tablets) or sevelamer (8 tablets).

– *Serum calcium level > 10 mg/dL*
  1. If PTH > 500 pg/mL, treatment with a calcium-mimetic agent should be started (reduction of target serum phosphorus by 15%). With iPTH 300-500 pg/mL, there are different opinions
  2. Aluminum hydroxide during a period of time that depends on P control and patient's characteristics
  3. Associate sevelamer or lanthanum carbonate

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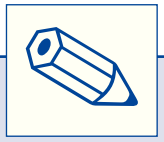

THE EDITOR'S NOTE

The treatment with phosphate chelating agents is, without a doubt, an open issue subject to controversy. We kindly invite the reader to participate by using the format Letters to the Editor.