Challenge of phosphorus control in hemodialysis patients: a problem of adherence?

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ABSTRACT

Objective: Few studies have investigated nonadherence to phosphate binders. The aim of this study was to evaluate the degree of adherence of our hemodialysis (HD) patients to phosphate binders and to determine which variables were related to nonadherence to treatment.
Methods: In 165 HD patients, the degree of adherence to the drugs prescribed was studied using the Simplified Medication Adherence Questionnaire.
Results: Of patients, 40% were nonadherent. Specific nonadherence to phosphate binder and hypotensive medication was admitted by 21% and 13% of patients, respectively. Nonadherent patients had significantly higher mean serum phosphorus (P) (4.7 ± 0.9 mg/dL vs. 4.4 ± 0.7 mg/dL; p=0.007) and potassium levels (6.3 ± 4.4 mEq/L vs. 5.3 ± 1.4 mEq/L; p=0.04). There was a statistically significant association between mean P levels >5.5 mg/dL in the last 6 months and nonadherence to treatment (X^2=4.8; 95% confidence interval [95% CI], 1.0-6.6; p=0.02). No relationship was found between patients with blood pressure levels >140/90 mm Hg and nonadherence to hypotensive medication (X^2=0.02; 95% CI, 0.2-4.1; p=0.88). Patients specifically nonadherent to phosphate binders were more likely to have P levels >5.5 mg/dL (X^2=4.7; 95% CI, 1.07-6.5; p=0.03). No statistically significant association was found between patients noncompliant with hypotensive agents and those noncompliant with phosphate binders (X^2=0.39; 95% CI, 0.4-4.7; p=0.53). There were no significant differences between adherent and nonadherent patients in terms of age, time on hemodialysis, Charlson Comorbidity Index, number of drugs prescribed and number of tablets per day (p>0.05).
Conclusion: Nonadherence to pharmacological treatment in dialysis patients is high. Nonadherence to phosphate binders was greater than for hypotensive agents, did not coexist in the same patients and had a greater impact on target achievement.

Key words: *Adherence, Compliance, Hypotensive agents, Phosphate binders, Phosphorus*

INTRODUCTION

The term *adherence* in health-related topics is defined as active, voluntary and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a desired therapeutic or preventive result, which implies the participation and commitment of the patient in their care (1). Nonadherence is one of the most frequent causes of apparent drug resistance, which should be considered in all cases of nonresponse to therapy. It is estimated that in developed countries up to 50% of drugs prescribed in chronic diseases are not taken as directed (2), and although different interventions aimed at improving adherence have been described (3), the problem does not have an easy solution (4).

In general, the highest levels of compliance are observed in treatments that require directly supervised medication (e.g., chemotherapy) and in illnesses with acute onsets. The lowest levels are seen in chronic patients in whom no immediate discomfort or risk is evident and in those in whom the treatment requires a change in lifestyle. Patients on hemodialysis would belong to this second group of patients and would therefore be more likely to show nonadherence to the treatments prescribed.

Successful control of phosphorus (P) is one of the key aspects in the management of dialysis patients (5-7), and it depends on several factors: dietary guidelines, attendance at hemodialysis sessions and medication prescriptions. However, numerous studies have revealed the difficulty in achieving P targets <5.5 mg/dL (8-10), despite the wide variety of drugs available for its treatment (11-15). In spite of this, few studies have investigated nonadherence to phosphate binders. From 1967 to 2006, only 13 studies reported rates of nonadherence to phosphate-binding medication. Articles were identified for review through the search of online databases PsycINFO (1967-2006), Medline (1950-2006), Embase (1980-2006) and CINAHL (1982-2006) (16); however, the underlying reasons for nonadherence are still not fully understood.

Lack of adherence may also influence the efficiency (cost-effectiveness ratio) of treatments because it prevents clinical effectiveness from being achieved with the smallest possible consumption of resources. The number of patients with chronic renal failure and renal replacement therapy shows an upward trend (17), and consumption of resources by this population is continuously increasing. In fact, in this regard, the emergence of increasingly more expensive phosphate binders (18) makes it indispensable to have a more detailed knowledge of the degree of adherence to these drugs and the causes determining it.

The primary objective of the present study was to evaluate the degree of adherence of our hemodialysis patients to phosphate binders. The secondary objectives were to compare adherence to phosphate binders with another relevant pharmacological group (hypotensive agents); to analyze the degree of concordance between adherence and its consequences (serum P and blood pressure levels) and between adherence to phosphate binders and the degree of non-pharmacological compliance (interdialytic weight gain and serum potassium [K] levels) and to determine which variables were related to nonadherence to treatment.

METHODS

This was a cross-sectional cohort study. The first part of the study evaluated the degree of overall adherence of the study population to the drugs prescribed using the Simplified Medication Adherence Questionnaire (SMAQ), and the second part focused specifically on adherence to phosphate binders.

The study included 165 patients, of whom 63% were male, with a mean age of 65.2 ± 14.7 years and mean time on hemodialysis of 155.6 ± 193.2 months (range 3.75-931.5 months). All patients underwent regular hemodialysis sessions lasting from 3.5 to 4 hours, 3 times per week, using 1.8-2.1 m^2 polysulfone dialyzers of high and medium permeability.

The median Charlson Comorbidity Index was 8 (P25-P75: 6-10). Of the study population, 14.2% had a moderate to severe degree of functional dependency. Nine patients who were unable to answer the questionnaire because of dementia or deafness were excluded. A total of 121 patients (73.3% of the total study population) answered a specific questionnaire related to preferences for phosphate binders. The data were collected from February to March 2007.

The mean (±SD) number of drugs prescribed per day in this population was 9.8 ± 3.0 and mean number of tablets per day was 18.6 ± 7.9, of which 51% were in the form of phosphate binders (mean tablets per day: 9.5 ± 6.0); 7.2 % (12/165) of patients were not prescribed any phosphate binder, 44.2% were taking a single agent, and 48.4% were receiving a combination of various binders (38.7% received 2 binders and 9.6% received 3 binders). Seventy-one patients (43%) were receiving vitamin D (alphacalcidol), all of them intravenously at the end of each hemodialysis session (3 times per week). The mean dose of vitamin D employed was 3.12 ± 1.94 µg/week.

Adherence assessment methods

Adherence to treatment was measured using the SMAQ (Tab. I), which has been validated in the Spanish popula-

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TABLE I
SIMPLIFIED MEDICATION ADHERENCE QUESTIONNAIRE

1. Do you ever forget to take your medication?	Yes	No
2. Do you always take the drugs at the indicated time?	Yes	No
3. Do you ever stop taking the drugs if you feel ill?	Yes	No
4. Did you forget to take the medication on the weekend?	Yes	No
5. In the last week, how many times did you not take any dose?	A: none B: 1-2 times C: 3-5 times D: 6-10 times E: more than 10 times	
6. Since the last visit, on how many complete days did you not take the medication?	Days: ….	

Patient is considered nonadherent if any of these conditions is met: 1: yes; 2: no; 3: yes; 4: yes; 5: C, D or E; 6: more than 2 days. The questionnaire is dichotomous; any response in the sense of noncompliance is considered nonadherent.

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tion for patients with AIDS (19). The response options are dichotomous; any response in the sense of noncompliance was considered nonadherent. Specific adherence regarding the 2 pharmacological groups studied was assessed using a specific questionnaire in which patients were asked about adherence to phosphate binders and hypotensive agents.

Measurement of clinical consequences of nonadherence

The consequence of nonadherence to phosphate binders was measured indirectly by determination of serum P. P levels were measured by UV spectrometry (normal range 2.7-4.5 mg/dL). Noncompliance with the P target was considered to occur when the mean of the monthly P levels measured in the last 6 months exceeded 5.5 mg/dL, based on recommendations of the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (20). The consequence of noncompliance with hypotensive medication was estimated by assessment of predialysis blood pressure levels in the short period of the last 4 weeks of dialysis sessions. Noncompliance with the blood pressure (BP) target was considered to occur when mean systolic BP pressure was greater than 140 mm Hg and/or mean diastolic BP was greater than 90 mm Hg or mean BP (MBP) was greater than 105 mm Hg.

Measurement of nonpharmacological compliance

The degree of nonpharmacological treatment compliance was assessed by measurement of interdialytic weight gain (IWG) (measured in short and long interdialytic periods) and bimonthly potassium (K) levels. Nonpharmacological noncompliance was considered when IWG was greater than 1.5 kg in the short period and greater than 3.0 kg in the long period, and/or mean K levels >6 mEq/L in the previous 6 months. We also considered the cutoff in the IWG corrected for body weight based on the most frequently values used in the literature: IWG >5.7% of dry body weight (21) and IWG >4% of dry body weight (22). K levels were measured by UV spectrometry (normal range 2.7-4.5 mg/dL). The percentage of monthly dialysis sessions attended by the patient was registered.

Related variables

Possible factors associated with lack of adherence were investigated by analyzing the following variables that may affect compliance: age, sex, time on hemodialysis, Charlson Comorbidity Index (23), degree of functional dependency as measured by Delta Test (24) (depending on the scores

obtained on each of the questionnaires corresponding to physical deficiency and mental dependency, a grading was obtained that provided guidance on the origin of the degree of dependency: score 0-4 = no deficiency or mild deficiency, score 5-9 = moderate deficiency, and score 10-15 = severe deficiency),number of drugs prescribed, number of tablets prescribed per day, and number of tablets prescribed per day in the form of phosphate binders.

We included the assessment of normalized protein catabolic rate (nPCR), as an indirect measure of protein ingestion, the second-generation Daugirdas Kt/V as a measure of adequacy of dialysis, and the concomitant prescription of vitamin D, so as to analyze the possible influence of these factors on the phosphate serum levels.

Statistical analysis

Statistical analysis was performed with SPSS 12 software. Student's t-test was used for paired samples of normally distributed data and the Wilcoxon test for non-normally distributed data. Qualitative variables were compared using the chi-square test. The comparison between the variables and adherence was done using an ANOVA test. To evaluate the possible influence of each of the independent variables on the adherence to phosphate binders, we used logistic regression analysis. The dependent variables were (i) the degree of adherence to phosphate binders as measured either by the SMAQ or (ii) the specific phosphate binders questionnaire and (iii) the mean levels of serum phosphate. Independent variables were age, time on dialysis, comorbidities, use of vitamin D, the number of different kind of oral medications prescribed daily, the number of pills/tablets prescribed daily and the total number of binders.

The level of statistical significance was considered to be $p<0.05$.

RESULTS

Simplified Medication adherence questionnaire

According to the SMAQ, 40% (66/165) of evaluated patients were defined as nonadherent to 1 of the treatments prescribed. A mean P level >5.5 mg/dL in the 6 months prior to the study was found in 13.9% (23/165) of patients; 7.2% of them (12/165) had a mean P level >6 mg/dL.

In 23.6% of patients, systolic BP levels were >140 mm Hg, and in 0.6% diastolic BP levels were >90 mm Hg predialysis. Of patients, 12.1% had an MBP greater than 105 mm Hg. In 62.4% of patients, IWG in the short period was >1.5 kg, and

in 35.1% the weight gain in the long period was >3.0 kg. The percentage of patients with IWG >5.7% of body weight (at weekends) was 13.3%, and 3.07% in midweek; the percentage of patients with IWG >4% of dry body weight (at weekends) was 50.9%, and 16.9% in midweek. Serum K levels were greater than 6 mEq/L in 40.6% of patients.

The percentage of patients with mean serum P >5.5 mg/dL was significantly higher in the group of nonadherent patients, according to the SMAQ; mean serum P and K levels were also significantly higher in this group as compared with the group of adherent patients (Tab. II). No statistically significant association was found between patients nonadherent to treatment according to the SMAQ and a mean K level >6 mEq/L in the last 6 months (X^2=2.8; 95% CI, 0.9-3.2; p=0.09), a weight gain over the week >1.5 kg (X^2=0.9; 95% CI, 0.7-2.6; p=0.32), a weight gain over the weekend >3 kg (X^2=1.6; 95% CI, 0.7-2.9; p=0.20), systolic BP >140 mm Hg (X^2=0.8; 95% CI, 0.6-2.8; p=0.36) or diastolic BP >90 mm Hg (X^2=0.6; 95% CI, 0.5-0.6; p=0.4). There was, however, a statistically significant association between mean P levels (>5.5 vs. ≤5.5 mg/dL) in the last 6 months and nonadherence to treatment according to the SMAQ (X^2=4.8; 95% CI, 1.0-6.6; p=0.02). Of the 71 patients receiving vitamin D, only 7% (5 patients) had a mean serum P >5.5 mg/dL. Treatment with vitamin D was significantly associated with a mean serum P <5.5 mg/dL (X^2=4.0; CI 95%, 0.1-0.9; p=0.02). All patients had 100% compliance with attendance at prescribed dialysis sessions.

Table III shows the factors associated with adherence, as measured by the SMAQ. There were no differences between women and men in adherence according to the SMAQ (relative risk [RR] =0.004; 95% CI, 0.5-1.9; p=0.94). A severe degree of dependency was not shown to be a risk factor for nonadherence either (X^2=2.1; 95% CI, 0.7-5.2; p=0.13). Logistic regression analysis showed that none of those variables was independently associated with nonadherence according to the SMAQ.

Table IV shows the factors associated with achievement or not of the P target <5.5 mg/dL. Similar results (not shown) were obtained when using the percentage of serum P determinations that were >5.5 mg/dL, over the same period. Logistic regression analysis showed that none of those variables were independently associated with nonadherence according to serum P levels.

Specific adherence questionnaire for phosphate binders and hypotensive agents

The specific questionnaire on phosphate binders and hypotensive agents was answered by 121 patients (73.3% of the total study population). Specific noncompliance with phosphate binder or hypotensive medication was admitted by 21.4% and 13% of patients, respectively. When questioned about which drug they would not take if they had a choice, 53 patients would not stop any of the drugs they were taking (43.8%) and 12 patients would stop all of them (9.9%). The drug group that most patients would stop was phosphate binders (20.6%), followed by calcium resonium (4.9%), hypotensive agents (3.3%) and the rest (17.5%), distributed in smaller proportions between different drugs.

TABLE II
ADHERENT VS. NONADHERENT PATIENTS BASED ON THE SIMPLIFIED MEDICATION ADHERENCE QUESTIONNAIRE

	Adherent (n=99)	Nonadherent (n=66)	p Value
Percentage of patients with phosphorus >5.5 mg/dL (%)	39.1	60.9	0.02
Serum phosphorus (mg/dL)	4.4 ± 0.7	4.7 ± 0.9	0.007
Serum potassium (mEq/L)	5.3 ± 1.4	6.3 ± 4.4	0.04
SBP (mm Hg)	133.0 ± 19.9	132.5 ± 18.9	0.85
DBP (mm Hg)	69.7 ± 10.5	69.7 ± 9.0	0.98
Weekend weight gain (g)	2,695.7 ± 1,146.0	2,735.3 ± 1,147.4	0.83
Midweek weight gain (g)	1,948.7 ± 942.7	1,946.5 ± 877.2	0.98

Results are expressed as means ± SD.
DBP = diastolic blood pressure; SBP = systolic blood pressure.

TABLE III
FACTORS RELATED TO ADHERENCE OR NONADHERENCE TO TREATMENT ACCORDING TO THE SIMPLIFIED
MEDICATION ADHERENCE QUESTIONNAIRE

	Adherent (n=99)	Nonadherent (n=66)	p Value
Age	67.3 ± 14.0	62.6 ± 15.7	0.04
Time on hemodialysis	135.2 ± 155.3	186.3 ± 237.1	0.09
Charlson Comorbidity Index	8.5 ± 2.8	7.2 ± 2.7	0.005
No. of drugs prescribed per day	9.9 ± 3.0	9.6 ± 3.0	0.53
No. of tablets prescribed per day	17.7 ± 6.7	19.9 ± 9.2	0.07
No. of sevelamer tablets prescribed	5.2 ± 4.1	6.1 ± 4.4	0.29
No. of calcium acetate tablets prescribed	1.7 ± 2.3	3.6 ± 3.9	0.001
No. of aluminum binder tablets prescribed	0.5 ± 1.2	1.0 ± 2.0	0.03
Total no. of tablets prescribed in the form of phosphate binders	9.5 ± 5.1	13.0 ± 7.3	0.001

No relationship was found between patients with BP levels >140/90 mm Hg and patients who admitted they were nonadherent to hypotensive medication (X^2=0.02; 95% CI, 0.2-4.1; p=0.88). Patients specifically nonadherent to phosphate binders were more likely to have mean P levels >5.5 mg/dL (X^2=4.7; 95% CI, 1.07-6.5; p=0.03). We did not find a statistically significant association between patients noncompliant with hypotensive agents and those noncompliant with phosphate binders (X^2=0.39; 95% CI 0.4-4.7; p=0.53).

There were no significant differences between patients adherent and nonadherent to hypotensive drugs in terms of age, time on hemodialysis, Charlson Comorbidity Index, number of drugs prescribed and number of tablets per day (p>0.05).

TABLE IV
FACTORS RELATED TO ACHIEVEMENT OR NOT OF THE PHOSPHORUS (P) TARGET <5.5 mg/dL

	P <5.5 mg/dL (n=142)	P >5.5 mg/dL (n=23)	p Value
Age	67.1 ± 14.0	55.2 ± 16.1	0.0001
Time on hemodialysis	151.5 ± 192.6	181.0 ± 198.9	0.50
Charlson Comorbidity Index	8.3 ± 2.8	6.0 ± 2.4	0.0001
No. of drugs prescribed per day	9.7 ± 3.0	9.9 ± 3.2	0.81
No. of tablets prescribed per day	18.3 ± 6.8	23.9 ± 8.4	0.005
No. of sevelamer tablets prescribed	6.1 ± 3.9	8.9 ± 4.5	0.007
No. of calcium acetate tablets prescribed	2.0 ± 2.9	5.6 ± 3.4	0.0001
No. of aluminum binder tablets prescribed	0.5 ± 1.4	2.2 ± 1.9	0.0001
Total no. of tablets prescribed in the form of phosphate binders	5.4 ± 6.1	14.6 ± 8.2	0.0001

P <5.5 mg/dL and P >5.5 mg/dL refer to the mean of all monthly phosphorus level determinations.

Patients nonadherent to phosphate binders had less comorbidity (Charlson Comorbidity Index 7.2 ± 2.4 vs. 8.9 ± 2.8; p<0.001), were younger (59.9 ± 16.1 years vs. 70.6 ± 14 years; p<0.0001) and were taking a larger number of tablets per day (21.4 ± 8.3 vs. 16.8 ± 6.8; p<0.01), especially in the form of phosphate binders (11.4 ± 8.1 vs. 7.8 ± 5.8; p<0.01). In the logistic regression analysis, younger age (p<0.05) and higher levels of P (p<0.05) were independently associated with nonadherence to phosphate binders

DISCUSSION

In other diseases, the role of adherence in treatment response has been studied in depth, and consensus documents have been drawn up with recommendations to improve it (25). The degree of adherence to dialysis sessions (26), diet (27) or fluid intake (28) has been analyzed in the dialysis population, and it has been shown that this lack of adherence may be related to mortality (23). However, adherence to drugs in general and to phosphate binders in particular has not been sufficiently explored in this type of patients.

In our study, 40% of patients admitted nonadherence to the drugs prescribed, but this lack of adherence varied for the different types of drugs studied. Specific nonadherence to phosphate binders and hypotensive medications was admitted by 21% and 13% of patients, respectively. There is wide variability in the reported rates of nonadherence to phosphate binding medication, which range from 22% to 74% of patients, with a median of 50% (16). This may be partially attributed to the differences in the definition and the methods used to measure adherence in these studies. Serum P levels have been the most frequently used indicator of phosphate binder adherence; e.g., 79% of the studies in the review by Karamanidou et al (16). The use of serum phosphate levels to evaluate adherence has limitations since many other factors have an impact on such levels, such as adherence to diet restrictions and dialysis attendance, residual renal function, comorbidities, hypercatabolism, nutritional status, hormonal and acid-base status, type and intensity of dialytic treatment and concomitant prescription of calcitriol or its analogues (29). In our study a higher percentage of patients with a mean serum P >5.5 mg/dL were not receiving vitamin D; in fact, we found an inverse association between vitamin D treatment and the levels of serum P. That could partly be explained by the fact that, since one of the reasons to reduce treatment with vitamin D is the development of hyperphosphatemia, in our patients vitamin D was always stopped when a serum P >5.5 mg/dL was detected.

We decided to use a combination of methods to assess adherence: serum P levels, the answers to a general medication adherence questionnaire (SMAQ) and an specific questionnaire in which patients were asked about adherence to phosphate binders. We found that factors associated with those 3 dependent variables were similar. At the same time, a statistically significant association was found between mean P levels >5.5 mg/dL in the last 6 months and nonadherence to treatment according to both questionnaires. Such concordances appear to confer additional validity to the questionnaires used in this population, even in spite of all of the other possible confounding factors, as previously commented. Furthermore, the SMAQ shows sufficient internal consistency among hemodialysis patients (Cronbach's α in this study 0.70). Knobel et al (19) also demonstrated sufficient internal consistency (Cronbach's α=0.75) among HIV-infected patients and satisfactory reproducibility (overall agreement of 88.2%, kappa 0.74). The SMAQ may prove to be an adequate instrument for the assessment of adherence to treatment among hemodialysis patients and might be used in most clinical settings (19); it shows adequate levels of sensitivity and specificity, when compared with other more objective measures; it is reliable, easy to apply, short (time under 5 minutes) and inexpensive and the results appear to correlate strongly with important clinical outcomes. Adherence questionnaires require few resources and are economical and easily adapted to the characteristics of each center. Their main limitations result from the apparent simplicity of the method, as well as from their subjectiveness and relatively low sensitivity compared with more objective methods. To our knowledge, there is no validated questionnaire to evaluate the degree of adherence to medications specifically designed for hemodialysis patients. In our study, we used the SMAQ, which though not validated in the hemodialysis population, has been previously validated in other chronic disease groups of the Spanish population (19). Research in the use of adherence questionnaires is a topic in continuous evolution, it would be desirable to incorporate new instruments specifically designed for and validated in this type of patients.

The cutoff point used for determining adherence or nonadherence in phosphate levels is still controversial; in fact, the different studies that analyzed nonadherence used different values ranging between 5 and 7 mg/dL (16). Because the K/DOQI guidelines recommend target P levels <5.5 mg/dL, we preferred to use this cutoff point, since it is the objective of the nephrologist when adjusting phosphate binders (kind and dosage) as well as the objective transmitted to the patient when negotiating compliance. The cutoff for blood pressure (<140/90) was extrapolated from the general population, but we certainly need more randomized control stud-

ies to clearly identify the optimum blood pressure, which we know is influenced by many factors in hemodialysis patients. This may be one of the reasons for the lack of association between BP target achievement and adherence to BP medications, and it suggests that the degree of blood pressure control is not a useful surrogate for overall drug compliance. In fact in a recent study (30) in patients in hemodialysis, to maintain the blood pressure objective (<140/90) was associated with a higher risk of mortality. On the other hand, there was no association between the degree of nonpharmacological treatment compliance, as assessed by measurement of IWG (measured in short and long interdialytic periods) and bimonthly K levels, and phosphate binder compliance. There are many possible biases in these measurements, and one of them is the arbitrary cutoff values for IWG used to classify patients into adherent and nonadherent groups. It is for this reason that we used many different cutoff values: in spite of this, no association was found between fluid nonadherence and phosphate binder nonadherence.

Adherence is often assessed directly and subjectively in daily clinical practice. However, patients' adherence may be underestimated with this method when compared with other methods (31, 32). This prevents potentially nonadherent patients from being identified, which on the one hand, causes the opportunity to intervene in their behavior to be lost, and on the other, facilitates the adoption of highly empirical therapeutic approaches, frequently resulting in an unnecessary increase in the doses of the drugs prescribed due to theoretical lack of response to treatment, when the underlying reality is a lack of compliance. In our study, the patients who had the higher P levels and who admitted they were nonadherent to treatment were prescribed the highest doses of binders, which could be explained by a progressive increase in the doses prescribed by the physician to achieve the target, which does not obtain the expected results and increases the cost of treatment because it does not take into account possible underlying nonadherence (33). Increasing the number of prescribed pills does not seem to improve control and may come at the cost of poorer health-related quality of life (34). A better knowledge of this matter will permit us to act and improve the percentage of patients with serum P under control. In another study published by our group we showed that steps designed to increase adherence to phosphate binders contributed significantly to P control, independently of the kind of drug used (35).

Overtreatment could be a potential cause of nonadherence. In fact, in our study 5 patients had P values <3.5 mg/dL and they received a mean of 11.1 ± 10.4 tablets per day in the form of phosphate binders; this number of tablets was smaller than the number of tablets of phosphate binders prescribed to patients with P values >3.5 mg/dL (16.8 ± 9.5 tablets) although not significantly (p=0.19). In any case, this was a high number of tablets, and this could be proving to be an excessive prescription of phosphate binders, which in turn could be the cause and consequence of nonadherence.

Adherence to phosphate binders is not the only factor that has an influence on P levels, but there is no doubt that it is one of the factors implied in its control. In this study, underdialysis and differences in nutritional status or protein ingestion as causes of differences in P levels were reasonably ruled out by means of the equilibrated (Kt/Ve) Daugirdas equation and protein equivalent of nitrogen appearance (nPCR). On the other hand, limitations of the study include that the retrospective nature of the data cannot enable us to assume causality.

Adherence rates not only vary between individuals, but also for the same individual over time. Most people are noncompliant at some time; lack of adherence is a variable behavior, not a characteristic of the person (36). It has been shown that psychological factors play a key role in compliance (37). We did not analyze this aspect in our study, but in view of the high prevalence of anxiety and depression in patients on hemodialysis (38), psychological and psychiatric intervention should be regarded as an important part of standard care.

The profile of the patient nonadherent to phosphate binders was that of a young patient with fewer comorbidities and a higher number of prescribed tablets and phosphate binders. No clear or consistent associations were found between adherence and sociodemographic or other characteristics of the population, except for age (younger patients were more likely to be nonadherent than older patients) (16, 23, 24). It is possible that younger patients are less aware of the consequences of the disease or worse prepared to follow medical recommendations than older patients; in any case we can not rule out an influence of the differences in phosphate absorption with aging. On the other hand, it is possible that young people are generally responsible for taking their medications, and they decide when to take them or not, whereas older patients are frequently dependent on caregivers who can help or compel them to ingest prescribed drugs.

The complexity and demands of the treatment regimen influence lack of adherence. It has been shown that the number of doses per day is inversely related to adherence (39). Hemodialysis patients receive a high number of tablets per day, of which more than half were phosphate binders in our study. Interference with living habits, either in work hours or at certain times in the patient's social life, is the reason some of these patients stop taking the medication or do so at the wrong time. This occurs more often in younger than older patients who have less social life. Phosphate binders require a

very strict dosing regimen because they must be taken during or immediately after each meal at least 3 times daily, which are factors that could favor nonadherence to these drugs over others. A study conducted in AIDS patients (40) showed that the percentage of nonadherent patients increased considerably when the definition of adherence also took into account dietary considerations. In fact, a fourth of patients admitted that they did not take the medication when they went out or were with friends. However, complexity per se is not the main factor contributing to nonadherence. A large number of other factors affected adherence to prescription, including age, dependency and cognitive function, the number of tablets prescribed, the cost of filling prescriptions, potential side effects of tablets and differences in lifestyle. The key aspect is the extent to which treatment is tailored to the individual's habits, expectations, beliefs and preferences (41).

We can conclude that nonadherence to treatment is common in the population on hemodialysis; however, not all patients are noncompliant "in general," but rather appear to show a certain "selective" nonadherence to some types of drugs. Nonadherence to phosphate binders was greater than that for hypotensive agents, did not coexist in the same patients and had greater impact on target achievement. Phosphate binders cause greater interference with the individual's living habits and social life, which may have an influence on the lower adherence to this pharmacological group. Patient preferences about prescribed drugs should be investigated to achieve adequate adherence to treatment. On the other hand, being nonadherent to a drug does no mean that one is noncompliant with other aspects of treatment, and thus no association was found between adherence to phosphate binders and the degree of nonpharmacological compliance (IWG or serum K levels). In fact, the drug group chosen by patients, if they could stop taking any, was phosphate binders (20.6%), followed at a considerable distance by the next 2 groups chosen (calcium resonium and hypotensive agents) (4% and 3.3%, respectively). Alternative instruments to evaluate adherence that might be applicable to the hemodialysis population are necessary, and it is important to design further studies that might provide insights into how to improve patient's compliance and biochemical as well as patient-level outcomes.

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