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Phosphorus binders: preferences of patients on haemodialysis and its impact on treatment compliance and phosphorus control

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ABSTRACT

Introduction: Non-adherence to phosphate binding (PB) medication may play a role in the difficulty in achieving the targets for phosphorus. We have a wide armamentarium of PB but preferences of patients are poorly understood. **Objective:** to study the patients' preferences and beliefs regarding PB and their influence on adherence and serum phosphate. **Methods:** A cross-sectional cohort study was performed. A total of 121 hemodialysis patients answered a specific questionnaire in which they were questioned about adherence, the type of PB they preferred and the reasons for their choice. All patients questioned tasted two or three PB. The consequence of non-adherence to PB was estimated indirectly by determination of serum phosphorus. **Results:** Specific noncompliance with PB medication was recognized by 21.4% of patients. Patients non-adherent specifically to PB were more likely to have P levels >5.5 mg/dl (χ^2: 4.7; 95% CI 1.07-6.5; P = 0.03). Paradoxically, patients non-adherent showed greater knowledge of the use (χ^2: 17.3; 95% CI -2.2-10.1; P <0.0001) and importance of the drug (χ^2: 10.4; 95% CI -1.5-6.6; P = 0.001). The percentage of patients prescribed binders they did not like was 54.5%. Patients who were taking PB they did not like had a greater risk of having P levels >5.5 mg/dl) (χ^2: 13.3; 95% CI -1.1-1.5; P = 0.0001). Calcium acetate was the prefered PB in 47.1% of patients, lanthanum carbonate in 40%, sevelamer in 20.6% and aluminum hydroxide in 19.4%. The reasons claimed by patients for their negative ratings of PB were the type of dosage form, the taste, the number of tablets and gastric intolerance. Gastric intolerance and bad taste were more frequent in aluminum hydroxide patients (19.4% and 22.2%, respectively). Sevelamer received complaints about its dosage form because the tablets were too large and a large number of tablets were required (27.2%). 17.7% of patient who were taking lanthanum carbonate did not like the chewable tablets. ***Conclusion:*** patients who were taking binders that they did not like had worse serum P levels and were prescribed higher doses of binders. Knowing patients' preferences about the drugs prescribed may be a key factor in achieving adequate adherence to treatment.

Key words: Phosphate binders. Preferences. Adherence to treatment. Hemodialysis

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Captores del fósforo: preferencias de los pacientes en hemodiálisis y su repercusión sobre el cumplimiento del tratamiento y el control del fósforo

RESUMEN

Introducción: *En la actualidad disponemos de un amplio abanico de captores del fósforo (CF), pero sabemos poco acerca de las preferencias de los pacientes y de su repercusión sobre el cumplimiento del tratamiento y el control de los niveles de fósforo.* ***Objetivo:*** *Estudiar las preferencias y creencias de los pacientes respecto a los CF, y su influencia sobre el cumplimiento del tratamiento y el control de los niveles de fósforo.* ***Pacientes y métodos****: Estudio observacional transversal. Se incluyeron 121 pacientes que respondieron un cuestionario genérico de cumplimiento del tratamiento (SMAQ) y a un cuestionario específico sobre cumplimiento del tratamiento con CF, tipo de CF preferido y razones de dicha preferencia. Todos los pacientes entrevistados habían probado dos o tres CF. Las consecuencias de la falta de cumplimiento del tratamiento con CF se estimaron indirectamente analizando los valores promedio de fósforo sérico.* ***Resultados:*** *El 40% de los pacientes era incumplidor según el cuestionario SMAQ; se encontró una asociación estadísticamente significativa entre la falta de cumplimiento*

en general y no alcanzar el objetivo de fósforo sérico promedio <5,5 mg/dl (OR = 4,8; IC 95%, 1,0-6,6; P = 0,02). El 21,4% de los pacientes reconocía un incumplimiento específico para los CF; estos pacientes presentaban una mayor probabilidad de tener cifras medias de fósforo >5,5 mg/dl (OR = 4,7; IC 95%, 1,1-6,5; P = 0,03). Un 43,8% de los pacientes no refirió tener preferencias entre los diferentes tipos de CF; para el resto de pacientes, el CF preferido fue Royen®, seguido de Fosrenol®, Renagel® y Pepsamar®. Las razones expresadas para el desagrado con el Renagel® fueron las siguientes: incomodidad en la toma por su gran tamaño (28,8%), necesidad de tomar muchos comprimidos y gran consumo de agua (57,7%) e intolerancia gástrica (13,3%). En el caso del Fosrenol®: incómodo de tomar (72,7%) e intolerancia gástrica (27,2%); para el Pepsamar®: mal sabor (54,5%) e intolerancia gástrica (45,4%). Sólo al 9,4% no le gustaba el Royen®. Al analizar los conocimientos de los pacientes respecto a la utilidad de los CF, un 42% sabía que servían para controlar el fósforo; un 52% no lo sabía y un 6% tenía ideas equivocadas. En cuanto a su importancia: un 47% no conocía por qué son importantes; un 2% tenía ideas erróneas; un 9% creía que era beneficioso para la salud; un 11% creía que era bueno «porque lo dice el medico»; un 26% porque controla el fósforo y un 5% lo relacionaba con el hueso. Ningún paciente relacionó los CF con la enfermedad cardiovascular. Un 24,4% no se llevaba los CF cuando salía fuera de casa o estaba con los amigos; eran pacientes más jóvenes a quienes se les habían prescrito un mayor número de comprimidos de CF y que presentaban un mayor riesgo de no cumplir el objetivo de fósforo (OR = 10,5; IC 95%, –1,8 a 16,4; P <0,001). El porcentaje de pacientes a quienes no les gustaba el CF prescrito fue del 54,5%; dichos pacientes presentaban un mayor riesgo de tener niveles séricos de fósforo >5,5 mg/dl (OR = 13.3; IC 95%, 1,1-1,5; P = 0,0001). Paradójicamente, los pacientes que no cumplían con el tratamiento demostraban un mejor conocimiento de su uso (OR = 17,3; IC 95%, 2,2-10,1; P <0.0001) e importancia (OR = 10,4; IC 95%, 1,5-6,6; P = 0,001). ***Conclusión:*** *Los pacientes a los que se les habían prescrito CF que no les gustaban tenían un peor control de los niveles de fósforo sérico y se les habían recomendado dosis más altas de los fármacos. El conocimiento de las preferencias de los pacientes acerca de las medicaciones que se les prescriben puede ser un factor esencial para conseguir un mayor cumplimiento del tratamiento y, por ende, lograr mejores resultados en la consecución de los objetivos terapéuticos.*

Palabras clave: *Captores del fósforo. Preferencias. Cumplimiento del tratamiento. Hemodiálisis*

INTRODUCTION

Phosphorus (F) control in patients on haemodialysis constitutes one of the most important issues facing nephrologists today. Various studies have demonstrated the difficulty of achieving the goal of F proposed by the K/DOQI (P <5.5 mg/dL) [1-3] and its impact on morbidity and mortality.[4-6] Additionally, the goals for phosphorus control are steadily becoming more ambitious and, in fact, figures are being proposed that come ever closer to normal levels.[6]

In all likelihood, the lack of compliance with phosphorus binder (PB) treatment plays an important role in the difficulty in achieving the objectives of serum phosphorus level control,[7] although the causes for this are not clearly understood.

PBs present certain characteristics that distinguish them from other drugs, in particular, they have to be taken with food and their interference with an individual's lifestyle and social habits impacts on the lack of treatment compliance.[8] A study performed on AIDS patients[9] showed that the percentage of patients who did not comply with the treatment increased considerably when the definition of compliance also took dietary considerations into account.

Today we have a wide array of PBs[10-14] with different presentations and characteristics. One key concept is to understand in what measure each of the different types of PB is adapted to an individual's habits and behaviour as well as their expectations, beliefs and preferences.[15] The emergence of increasingly expensive PBs[16] makes non-compliance have a significant economic impact, given that it affects the efficiency (cost-effectiveness) of treatments, which hinders achieving clinical effectiveness with the lowest consumption of resources possible.

The aim of this study was to expand our understanding of patients' preferences and beliefs regarding PBs and their influence on compliance and in achieving therapeutic goals.

PATIENTS AND METHODS

This was an observational transversal study. A total of 121 out of 165 dialysis patients from our unit were included. Forty-four patients were excluded from the study: 9 patients were unable to answer the questionnaire due to dementia or significant hearing loss; 12 patients were not prescribed PBs and 23 took a single PB, which prevented comparison with other types of binders.

The 121 patients who were receiving a combination of two (85 patients) or three PBs (36 patients) answered a questionnaire specifically related to their preferences regarding the PBs. The specific questions about PBs referred to drugs that the patients regularly took (more than 3 months of treatment). Thirty-six patients took three types of PB: aluminium hydroxide (Pepsamar®), calcium acetate (Royen®) and sevelamer (Renagel®). Eighty-five patients took two: calcium acetate (Royen®) and sevelamer (Renagel®). In

January 2008, 45 patients who previously had been treated with high doses of sevelamer had their medication changed to lanthanum carbonate (Fosrenol®), which allowed this new medication to be included in the preferences analysis along with the rest of the PBs after having been used for at least two months by the patient. Data was collected between March and April 2008.

Sixty-three percent of the patients were men with a mean age of 64.8 ± 14.2 years and a mean time on haemodialysis of 154.6. ± 192.4 months (3.74 to 931.5 months). The median Charlson comorbidity index was 8 (P25-P75: 6-10).

The average number of daily drugs prescribed for this population was 9.8 ± 3.0 and the average number of daily tablets was 18.6 ± 7.9, of which 51% were in PB form (average number of daily PB tablets: 9.5 ±6.0). All patients had 100% compliance for attending the prescribed dialysis sessions. The average number of daily tablets for patients taking calcium acetate (Royen®) was 4.9 ± 2.9; 3.4 ± 1.7 for aluminium hydroxide (Pepsamar®); 7.1 ± 3.5 for sevelamer (Renagel®); and 3.0 ± 0.0 for lanthanum carbonate (Fosrenol®).

Methods for assessing treatment compliance

In general, drug treatment compliance was measured using the SMAQ compliance questionnaire, which has been validated for the Spanish AIDS population[17] (Table 1). The answer choices were dichotomous; any response leaning toward non-compliance was considered as not following treatment. This questionnaire has been shown to have sufficient internal consistency (Cronbach's alpha = 0.75) in patients infected with HIV, it is easily reproducible (overall agreement 88.2%; kappa = 0.74)[17] and it has been shown to have sufficient internal consistency in haemodialysis patients (Cronbach's alpha for this population = 0.70).[8] The specific compliance with PB treatment was analysed by means of a specific non-validated questionnaire that asked about PB treatment compliance, the preferred type of PB and the reasons why, the least-liked type of PB and the reasons why, as well as a series of questions about their knowledge of the usefulness and importance of the drug ("What use have PBs?", "Why do you think they are important?") and about patient habits (outings, social life).

Measurement of clinical consequences of non-compliance

The consequences of non-compliance with PB treatment were estimated indirectly by determining serum phosphorus levels. Failure to reach the objective occurred when the average for all monthly phosphorus measurements performed in the last 6 months exceeded 5.5 mg/dl. Phosphorus levels were measured using UV spectrometry (normal range 2.7 to 4.5 mg/dl).

Related variables

We studied possible factors associated with the lack of compliance, and analysed the following variables that might affect it:

1. Age.
2. Sex.
3. Time in haemodialysis.
4. Charlson co-morbidity index.[18]
5. Number of drugs prescribed.
6. Number of tablets per day prescribed.
7. Number of PB tablets per day prescribed.
8. Degree of acceptance of each type of PB. Patients were questioned about which PB they preferred and which they liked the least and the reasons why.
9. Knowledge of the usefulness of the drug and its importance.
10. Influence of habits (outings, social life).

Table 1. SMAQ Compliance questionnaire

1. Have you ever forgotten to take your medication?	☐ Yes ☐ No
2. Do you always take your drugs on time?	☐ Yes ☐ No
3. Have you ever stopped taking the drugs because you felt sick?	☐ Yes ☐ No
4. Did you forget to take your medication on the weekend?	☐ Yes ☐ No
5. How many times did you not take a dose last week?	A: 0
	B: 1-2
	C: 3-5
	D: 6-10
	E: more than 10
6. How many full days since the last visit did you not take the medication?	Days: ….

Statistical analysis

The statistical analysis was performed using SPSS 12.1. We used the Student's t-test for the comparison of independent samples when the data followed a normal distribution. For those cases in which the data did not, we used the Wilcoxon test. The qualitative variables were compared using the chi-squared test and the extent of the association was quantified using the odds ratio calculation with a confidence interval of 95%. Logistic regression analysis was used in order to evaluate the possible influence of each of the independent variables on PB treatment compliance. The dependent variables were the degree of compliance estimated with the SMAQ questionnaire, the degree of PB treatment compliance estimated with the specific questionnaire, and the average serum phosphorus levels. The independent variables were age, time on haemodialysis, comorbidity, use of vitamin D, the number of different types of oral medication prescribed daily, the number of tablets prescribed daily and the total number of PB tablets. Statistical significance was considered to be at $P < 0.05$.

RESULTS

SMAQ COMPLIANCE QUESTIONNAIRE

According to the SMAQ compliance questionnaire, 40% (49/121) of the patients assessed were defined as not following some of the prescribed treatments.

In the 6 months prior to assessing compliance, 14% of patients studied (17/121) had an average phosphorus level > 5.5 mg/dl and 7.4% (9/121) had >6 mg/dl. The 39.1% of patients who complied with treatment and 60.9% of those who did not had serum phosphorus levels > 5.5 mg/dl (OR = 4.8; IC 95%, 1.0-6.6; P = 0.02). The grouP of patients that did not comply with the treatment according to the SMAQ questionnaire had an average serum phosphorus level significantly higher than the group of patients that complied with the treatment (4.7 ± 0.9 versus 4.4 ± 0.7; P <0.01).

There were no significant differences in the averages for Kt/V and nPCR between patients with P >5.5 mg/dl (1.45 ± 0.54 and 1.0 ± 0.5 g/dl, respectively) and with P <5.5 mg/dl (1.46 ± 0.54 and 1.1 ± 0.4 g/dl, respectively)

Questionnaire for specific compliance for phosphorus binders

Some 21.4% of the patients admitted non-compliance with therapy specifically for PBs. When questioned about which drug they would not take if they could choose, 53 patients said they would not stop taking any of the drugs they were taking (43.9%) and 12 patients said they would stop them all (9.9%). The group of drugs that the largest percentage of patients would choose to stop taking were the PBs (20.6%), followed by Resincalcio® (4.9%) and the hypotensive drugs (3.3%). The rest (17.5%) corresponded to other types of drugs in smaller rates.

Patients who specifically did not comply with the PB treatment had a greater probability of having average phosphorus readings >5.5 mg/dl (OR = 4.7; IC 95%, 1.07-6.5; P = 0.03). Table 2 shows the factors related to lack of PB treatment compliance.

The logistic regression analysis showed that none of the independent variables (age, time on haemodialysis, comorbidity, use of vitamin D, the number of different types of oral medication prescribed daily, the number of tablets prescribed daily and the total number of PB tablets) were independently associated with a lack of overall or specific compliance or with the average levels of serum phosphorus.

Table 2. Factors related to treatment compliance or non-compliance of treatment with phosphorus binders (n = 121)

	Compliant with PB (n = 95)	Not compliant with PB (n = 26)	p
Age	67.1 ± 14.0	55.2 ± 16.1	0.0001
Time in haemodialysis	151.5 ± 192.6	181.0 ± 198.9	0.50
Charlson co-morbidity index	8.3 ± 2.8	6.0 ± 2.4	0.0001
Number of drugs prescribed per day	9.7 ± 3.0	9.9 ± 3.2	0.81
Number of tablets prescribed per day	18.3 ± 6.8	23.9 ± 8.4	0.005
Number of sevelamer tablets prescribed	6.1 ± 3.9	8.9 ± 4.5	0.007
Number of calcium acetate tablets prescribed	2.0 ± 2.9	5.6 ± 3.4	0.0001
Number of aluminium chelating tablets prescribed	0.5 ± 1.4	2.2 ± 1.9	0.0001
Total number of phosphorus binder tablets prescribed	5.4 ± 6.1	14.6 ± 8.2	0.0001

Table 3. Patient prefences with respect to phosphorus binders

	Preferred binder	Least favourite binder	Not defined
Calcium acetate (Royen®)	29/61 (47.5%)	7/61 (11.4%)	25/61 (40.9%)
Lanthanum carbonate (Fosrenol®)	18/45 (40%)	11/45 (24.4%)	16/45 (35.5%)
Sevelamer (Renagel®)	20/97(20.6%)	42/97 (43.2%)	35/97 (36%)
Aluminium hydroxide (Pepsamar®)	5/27 (18.5%)	11/27 (40.7%)	11/27 (41%)

Preferences, knowledge and habits relating to phosphorus binders

Some 43.8% (53/121) of the patients had no preferences for any particular PB and 6.6% (8/121) did not reply to this item in the survey. Some 54.5% of the patients had a PB prescribed that they did not like. Table 3 lists the preferences of the patients for the different types of binders and Table 4 shows the reasons justifying them.

Some 24.4% of patients did not take the medication when leaving the house or staying with friends, posing a greater risk of not meeting the goal of P < 5.5 mg/dl (OR = 10.5; IC 95%, 1.8-16.4; P < 0.001). These patients were younger (59.3 ± 15.8 versus 66.8 ± 14.5; P <0.01) and had a greater number of daily PB tablets (12.03 ± 7.9 versus 8.7 ± 5.5; P <0.01)

Patient knowledge and beliefs about the usefulness and importance of PB are shown in Table 5.

Patients who took a PB that they did not like had a higher risk of having P readings that were out of control (>5.5 mg/dl) (OR = 13.3; IC 95%, 1.1-1.5; P = 0.0001). Paradoxically, patients who did not comply with phosphorus binder treatment had a better understanding of the usefulness (OR = 17.3; IC 95%, 2.2-10.1; P <0.0001) and importance of the drug (OR = 10,4; IC 95%, 1.5-6.6; P = 0001).

DISCUSSION

Compliance with CKD treatment in its various aspects is essential and a large part of its results depend on it. This study shows a lack of treatment compliance with prescribed drugs in haemodialysis patients that reaches 40%. In 21% of cases, there was a specific lack of compliance for PB, which was associated with higher average serum phosphorus levels. There are few references that address this issue specifically and the data reported vary, according to the studies, between 22 and 74% of patients, with a median of 50%.[7,19] It is well known that the lowest compliance levels are observed in chronic patients in whom there is no discomfort or immediate risk and in whom the treatment requires a lifestyle change. Patients with CKD belong to this group of patients.[20]

The factors that determine treatment compliance in general are diverse. Firstly, clear and consistent relationships have not been found between compliance and socio-demographic variables or population characteristics[7] except in the case of age (young patients are more likely not to comply). The profile of a patient that does not comply with PB treatment was a young patient with lower comorbidity and a greater number of PB tablets prescribed.

What has been demonstrated is that the complexity and demands of the treatment regimen influence the lack of

Table 4. Reasons for justifying not taking various phosphorus binders

	Total number of patients treated	Gastric intolerance n (%)	Does not like the type of presentation n (%)	High number of tablets n (%)	Bad taste n (%)
Renagel®	121	8 (6.6%)	16 (13.2%) (tablets are too large)	33 (27.2%)	0 (0%)
Fosrenol®	45	3 (6.6%)	8 (17.7%) (chewable tablets)	0 (0%)	0 (0%)
Pepsamar®	36	6 (19.4%)	0 (0%)	0 (0%)	8 (22.2%)
Royen®	121	6 (4.9%)	0 (0%)	4 (3.3%)	4 (3.3%)
Total	323	23 (7.1%)	24 (7.4%)	37 (11.4%)	12 (3.7%)

compliance; consequently, the number of daily doses is inversely proportional to the level of compliance and this, in turn, is associated with a lower patient quality of life.[19] Patients on haemodialysis are prescibed a high number of daily tablets of which, in our study, more than half are PBs. Thus, in a previously conducted study by our group,[22] with 51 patients with difficulty controlling phosphorus and who received large doses of sevelamer (more than 9 tablets/day), changing sevelamer for 3 daily tablets of lanthanum carbonate helped achieve a better control of serum phosphate (the percentage of patients with serum phosphate <5.5 mg/dl increased from 46.9 to 72.5%; p<0.01). The reduction in the number of tablets may somehow influence patient compliance with treatment and therefore, produce better clinical outcomes, as other studies have suggested.[19]

Interference with daily habits, whether during work hours or within the context of a patient's social life, may motivate some of them to stop taking medication or to take it at the wrong time. This occurs more frequently with young patients who have a more active social life. PBs require a very strict dosage regimen since they must be taken during or immediately after each meal and, generally, three times a day, which may be a factor in promoting non-compliance with treatment with these drugs as opposed to other drugs.[8,19] Indeed, a quarter of our patients admitted not taking the medication when out of the house or when being with friends. A study performed on AIDS patients[23] showed that the percentage of patients that did not comply with treatment increased considerably when the definition of compliance also took dietary considerations into account.

Simplifying the therapy regimen has a certain positive effect but does not solve the problem of non-compliance since it is not the only factor involved. Another factor involved, which was not analysed by our study but should be the subject of future research, was the influence of the amount of time a patient had been taking a particular type of binder, since taking a certain medication for a long period of time may cause the patient to tire of doing so. In this sense, lanthanum carbonate may have a certain "advantage" in our study since it was introduced only two months prior to its initiation. For example, in our previously-mentioned study on the conversion from sevelamer to lanthanum carbonate, after 12 months and despite the potential advantages in reducing the number of tablets, 31% of patients preferred to go back to sevelamer.[20]

Additionally, an adequate understanding of the drugs' actions may positively influence compliance. Our study demonstrated the significant lack of knowledge about the usefulness and importance of PBs. Almost half of the patients studied did not know what the drugs were for or the extent of their importance. Not one patient related these drugs with cardiovascular disease. Adequately conveying the importance of these drugs is essential and may contribute to increasing treatment compliance.[24] However, knowledge *per se* does not ensure compliance. In fact, non-compliant patients taking PB show, paradoxically, a greater knowledge of their use and importance, possibly due to dealing with patients who, faced with the lack of phosphorus control, had been presssured more towards compliance and had received more explanations from the doctor. The influence of age cannot be ruled out, given that younger patients tend to better understand the indications of chelators.

It is known that a high percentage of patients quit treatment to avoid side effects, regardless of the clinical relevance that these may have, which means that drugs that frequently induce digestive symptoms may constitute a greater risk of non-compliance. In our population, digestive intolerance was among the negative side effects of PB, which include constipation, flatulence, nausea, abdominal discomfort and dyspepsia. The PB that most digestive symptoms were attributed to was aluminium hydroxide (18%), followed by lanthanum carbonate and sevelamer (6%). Calcium acetate caused the least number of adverse digestive symptoms (4%).

Table 5. Responses to questions related to beliefs about the usefulness and importance of phosphorus binders (n = 121)

	What is their use?	Why are they important?
To control phosphorus	40%	26%
For bones	2%	5%
For cardiovascular disease	0%	0%
Does not know	45%	40%
Does not answer	7%	7%
Misconceptions	6%	2%
Because the doctor says so	0%	11%
Because they are beneficial to health	0%	9%

More than half of the patients in our population did not like the PB they were prescribed, and patients who took a PB that they did not like had a higher risk of having F readings that were out of control (>5.5 mg/dl). Today we have a wide array of PBs with different characteristics. The majority of patients studied received various type of binders and almost half took two or more types. The PB most positively regarded among patients that took it was calcium acetate, followed by lanthanum carbonate, sevelamer and, finally, aluminium hydroxide. The reasons given by the patients for negatively rating the PBs were the form, taste, number of tablets and gastric intolerance. Sevelamer received complaints about its form for its excessively large tablets and for requiring a large number of them, which required the patient to ingest large quantities of water. Some 17.7% of patients that took lanthanum carbonate did not like the chewable form and, in fact, some elderly patients had trouble chewing them. Almost a quarter of the patients that took aluminium hydroxide reported unpleasant taste.

The first step required for improving therapy compliance is proper diagnosis of the problem. In some cases, certain objective parameters, such as the levels of phosphorus, will clearly indicate that we are faced with a case of non-compliance. Compliance is often subjectively assessed in clinical practice. This prevents the identification of many patients who may be non-compliant, missing the opportunity to intervene in their behaviour. This also facilitates the adoption of therapeutic attitudes with a high degree of empiricism, which in many cases causes an unnecessary increase in the doses of prescribed drugs. This is justifed by a theoretical lack of response to treatment even though the underlying truth is a lack of compliance.

The compliance questionnaires are tools that require few resources and are affordable and adaptable to the characteristics of each centre. Research on the use of compliance questionnaires is a continually advancing issue. It would be desirable to incorporate new instruments that are validated for these types of patients. The SMAQ questionnaire has been validated for HIV+ patients in the Spanish population but could also be used with CKD patients. In our study we decided to use a combination of methods to evaluate compliance: the average levels of serum phosphate and the responses to the SMAQ questionnaire on compliance with the medication in general and a specific non-validated questionnaire in which the patients were asked about their compliance with PBs. We found that the factors associated with these three dependent variables were similar, with a statistically significant association between patients with average levels of P >5.5 mg/dl in the previous months and the lack of treatment compliance in accordance with both questionnaires. These correlations seem to additionally validate the use of these questionnaires with patients on haemodialysis. Additionally, the SMAQ showed sufficient internal consistency in this group of patients (Cronbach's alpha = 0.70). Knobel et al[17] showed a similar internal consistency (Cronbach's alpha = 0.75) among HIV+ patients as well as a satisfactory reproducibility (88.2% overall agreement, kappa 0.74). The SMAQ can show its validity for evaluating treatment compliance in patients on haemodialysis: it shows adequate levels of sensitivity and specificity when compared to other more objective measurements; is correlated with phosphorus levels; is reliable; has sufficient internal consistency and reproducibility; is easy to apply (takes about 5 minutes); and is inexpensive.

Knowing the patients' preferences regarding the prescribed drugs may be another major factor in achieving good treatment compliance. It is important for both nephrologists and the industry to understand these aspects. The pharmaceutical industry, based on their knowledge of patient preferences, should try to develop drugs that adjust to these preferences and develop presentations that are better tolerated and that pass through the patients as unnoticed as possible. In addition, as long as there are no medical contraindications, nephrologists can use in each case those PBs that each patient prefers or combinations thereof in order to minimise side effects. Some authors have suggested[25] that a combination of low doses of different drugs may be a more cost-effective method to ensure tolerability, efficacy and compliance. In our study, patients who took binders that they did not like showed poorer control of serum phosphorus and were the ones prescribed the highest doses of PB. If lack of compliance is not explored, it is current practice for the doctor to increase the prescribed doses, which fails to achieve the objective.[19] The relationship that is established between health care providers and patients is of utmost importance. Trust, continuity, accessibility, flexibility and confidentiality are all factors that favourably influence compliance. Supervision of therapy compliance by the team that cares for the dialysis patient is a measure that may contribute favourably to patient compliance with the prescribed treatment. Probably one of the most important factors is providing detailed and realistic information, as well as joint decision making in a framework of mutual trust (patient-centered model).[26]

To summarise, short and long-term compliance is the result of a complex process that is developed through various stages: acceptance of the diagnosis, perception of the need to perform correct treatment, the motivation to do so, the provision and training of skills to carry it out, the capacity of overcoming the barriers and difficulties that may arise, and the maintenance of achievements over time. Treatment must be individualised and adapted to the needs and preferences of each patient. It is essential to understand the patient's daily habits, personal resources and family, and analyse their understanding of the disease and the degree of awareness and confidence they have in order to start the treatment. The assessment of possible risk factors for achieving an optimal treatment compliance should serve in planning specific

interventions for each patient, interventions that will generally be multifaceted and multidisciplinary.[27]

In conclusion, patients who took PBs that they found unpleasant, for various reasons, had poorer phosphorus control despite having a larger quantity of these drugs prescribed for them, which leads us to believe that the reason for this lack of control may lie in a lack of treatment compliance. A greater understanding of the patients' preferences, the use of different drugs in lower doses, a better doctor-patient relationship and detailed and accurate information as part of a joint decision-making process may be key factors in achieving phosphorus control objectives.[28,29]

ANNEX. QUESTIONNAIRE ON PHOSPHORUS BINDER PREFERENCES

1. Which of the medications that you take would you choose to drop?
2. Which of the medications that you take for controlling phosphorus (Pepsamar®, Royen®, Renagel® and Fosrenol®) do you like the most? Why?
3. Which of the medications that you take for controlling phosphorus (Pepsamar®, Royen®, Renagel® and Fosrenol®) do you like the least? Why?
4. Of the medcations you are taking for phosphorus, indicate which ones you like or dislike:

☐ Pepsamar® LIKE / DISLIKE
☐ Royen® LIKE / DISLIKE
☐ Renagel® LIKE / DISLIKE
☐ Fosrenol® LIKE / DISLIKE

1. What do you think these medications are for?
2. Why do you believe these are important to take?
3. When you leave the house or are with friends, do you still take the medications?

REFERENCES

1. Arenas MD, Álvarez-Ude F, Gil MT, et al. Application of NKF-K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease: changes of clinical practices and their effects on outcomes and quality standards in three haemodialysis units. Nephrol Dial Transplant 2006; 21:1663-8.[Pubmed]
2. Wei M, Taskapan H, Esbaei K, Jassal SV, Bargman JM, Oreopoulos DG. K/DOQI guideline requirements for calcium, phosphate, calcium phosphate product, and parathyroid hormone control in dialysis patients: can we achieve them? Int Urol Nephrol 2006;38:739-43.[Pubmed]
3. Lorenzo V, Martín-Malo A, Pérez-García R, Torregrosa JV, Vega N, De Francisco AL, et al. Prevalence, clinical correlates and therapy cost of mineral abnormalities among haemodialysis patients: a cross-sectional multicentre study. Nephrol Dial Transplant 2006;21(2):459-65.[Pubmed]
4. Young EW, Akiba T, Albert JM, et al. Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2004;44(5 Suppl 2):34-8.[Pubmed]
5. Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2005;67:1179-87.[Pubmed]
6. Rodríguez-Benot A, Martín-Malo A, Álvarez-Lara MA, Rodríguez M, Aljama P. Mild hyperphosphatemia and mortality in hemodialysis patients. Am J Kidney Dis 2005;46(1):68-77.[Pubmed]
7. Karamanodou C, Clatworthy J, Weinman J, Horne R. A systematic review of the prevalence and determinants of nonadherence to phosphate binding medication in patients with end-stage renal disease. BCM Nephrol 2008;31(9):2.
8. Arenas MD, Malek T, Gil MT, Moledous A, Álvarez-Ude F, Reig-Ferrer A. The challenge of phosphorus control in the hemodialysis patient: a problem of adherence? J Nephrol 2010. In press.
9. Nieuwkerk PT, Sprangers MAG, Burger DM, et al. Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. Arch Intern Med 2001;161:1962-8.[Pubmed]
10. Joy MS, Finn WF. Randomized, double-blind, placebo-controlled, dose-titration, phase III study assessing the efficacy and tolerability of lanthanum carbonate: a new phosphate binder for the treatment of hyperphosphatemia. Am J Kidney Dis 2003;42:96-107.[Pubmed]
11. Slatopolsky EA, Burke SK, Dillon MA, and the Renagel study group. Renagel, a nonabsorbed calcium- and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. Kidney Int 1999;55:299-307.[Pubmed]
12. Sechet A, Hardy P, Hottelart C, Rasombololona M, Abighanem O, Oualim Z, et al. Role of calcium carbonate administration timing in relation to food intake on its efficiency in controlling hyperphosphatemia in patients on maintenance dialysis. Artif Organs 1998;22:564-8.[Pubmed]
13. Arenas MD, Malek T, Moledous A, Núñez C, Álvarez-Ude F. Use of aluminum-based phosphate-chelators in hemodialysis in the era of ultrapure water. Nefrologia 2008;28(2):168-173.[Pubmed]
14. Sprague SM. A comparative review of the efficacy and safety of established phosphate binders: calcium, sevelamer, and lanthanum carbonate. Curr Med Res Opin 2007;23(12):3167-75.[Pubmed]
15. Goff SL, Mazor KM, Meterko V, Dodd K, Sabin J. Patients' beliefs and preferences regarding doctors' medication recommendations. J Gen Intern Med 2008;23:236-41.[Pubmed]
16. White CA, Jaffey J, Magner P. Cost of applying the K/DOQI guidelines for bone metabolism and disease to a cohort of chronic hemodialysis patients. Kidney Int 2007;71:312-7.[Pubmed]
17. Knobel H, Alonso J, Casado JL, Collazos J, González J, Ruiz I, et al. GEEMA Study Group. Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA study. AIDS 2002;16:605-13.[Pubmed]
18. Hemmelgarn BR, Manns BJ, Quan H, Ghali WA. Adapting the Charlson Comorbidity Index for use in patients with ESRD. Am J Kidney Dis 2003;42(1):125-32.[Pubmed]
19. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23(8):1296-310.[Pubmed]
20. Arenas MD, Rebollo P, Malek T, Moledous A, Gil MT, Álvarez-Ude F,

et al. A comparative study between two new phosphate binders (Sevelamer and Lanthanum Carbonate) in the routine clinical practice. J Nephrol 2010. In press.
21. Horne R, Buick D, Fisher M, Leake H, Cooper V, Weinman J. Doubts about necessity and concerns about adverse events: identifying the types of beliefs that are associated with non-adherence to HAART. Int J STD AIDS 2004;15:38-44.[Pubmed]
22. Lyons AC, Chamberlain K. Health Psychology: A Critical Introduction. Cambridge: Cambridge University Press, 2006.
23. Kammerer J, Garry G, Hartigan M, Carter B, Erlich L. Adherence in patients on dialysis: strategies for success. Nephrol Nurs J 2007;34(5):479-86.[Pubmed]
24. Ambrosioni E. Pharmacoeconomic challenges in disease management of hypertension. J Hypertens 2001;(Suppl):S33-S40.
25. Lyons AC, Chamberlain, K. Health Psychology: A Critical Introduction. Cambridge: Cambridge University Press, 2006
26. Kammerer J, Garry G, Hartigan M, Carter B, Erlich L. Adherence in patients on dialysis: strategies for success. Nephrol Nurs J 2007;34(5):479-86.[Pubmed]
27. Epstein RM, Peters E. Beyond information: exploring patients' preferences. JAMA 2009;302(2):195-7.[Pubmed]
28. Street RL, Makoul G, Arora NK, Epstein RM. How does communication heal? Pathways linking clinician-patient communication to health outcomes. Patient Educ Couns 2009;74(3):295-301.[Pubmed]

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