

# Use of aluminum-based phosphate-chelators in hemodialysis in the era of ultrapure water

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## SUMMARY

**Introduction:** Aluminium binder has been ill-advised, but his use remain applicable in the clinique practice in very seleccionated and particular patients. The repercussion of prolonged treatment with low doses of aluminium phosphate-binders in haemodialysis was studied. The haemodialysis unit had a double osmosis inverse and the aluminium levels in haemodialysis liquid was less than 2 microgrames/liter.

**Methods:** 41 patients of the 295 on haemodialysis received aluminium phosphate-binders since the 2005 january to the 2007 november. The mean time of treatment was 17.8 months, and the doses was 3.9 tablets day (mean of 463 g in the studied period). The association of low doses of aluminium phosphate-binders permitted a better control of phosphorus (6.8 to 4.8 mg/dl;  $p < 0.0001$ ), with a reduction of the others phosphate-binders: sevelamer (10.4 a 8 tablets/day;  $p < 0.0001$ ) and calcium phosphate-binders (4.6 to 3.1 tablets/day;  $p < 0.0001$ ). The serum aluminium increased after the aluminium treatment (6.8 to 13.8 mcg/l;  $p < 0.0001$ ), and no toxicity indirect signs were observed on CMV, haemoglobin, none PTH. Five patients (12.1%) reached aluminium serum levels higher 20 mcg/l, and none reached the 40 mcg/l.

**Conclusions:** The aluminium phosphate-binders were effective, economical and, now, with an apparent better security profile than in a previous time, but it is very important to be careful with this use and to follow a vigilance strict on patients and haemodialysis liquid.

**Key words:** Aluminium phosphate-binder. Haemodialysis. Phosphorus. Osmosis inverse.

## RESUMEN

**Introducción:** Aunque el hidróxido de aluminio haya sido desaconsejado, su utilización permanece vigente en la práctica clínica habitual, para pacientes concretos y muy seleccionados. Se analiza la repercusión que ha tenido el tratamiento prolongado con bajas dosis de captoreos aluminicos en una población de pacientes que se dializan en una unidad con doble sistema de ósmosis inversa y niveles de aluminio en el líquido de diálisis inferiores a 2 microgramos/litro.

**Material y métodos:** Cuarenta y un pacientes de 295 pacientes en hemodiálisis recibieron captoreos aluminicos desde enero de 2005 hasta noviembre de 2007. El tiempo medio de tratamiento fue  $17,8 \pm 14,6$  meses, y la dosis media fue  $3,9 \pm 2,29$  comprimidos al día (media de 463 g en el periodo estudiado). La asociación de captoreos del fósforo aluminicos a dosis bajas permitió un mejor control del fósforo (6,8 a 4,8 mg/dl;  $p < 0,0001$ ), con una reducción en las dosis de otros fármacos: sevelamer (10,4 a 8 comp/día;  $p < 0,0001$ ) y quelantes cálcicos (4,6 a 3,1 comp/día;  $p < 0,0001$ ). Los niveles de aluminio sérico aumentaron tras el tratamiento (6,8 a 13,8 mcg/l;  $p < 0,0001$ ), y no se observaron signos indirectos de toxicidad sobre el VCM, la hemoglobina ni la PTH. 5 pacientes (12,1%) alcanzaron unos niveles de aluminio superiores a 20 microgramos/l, y en ningún caso este valor alcanzó los 40 microgramos/l.

**Conclusiones:** Los ligantes del fósforo aluminicos se ha mostrado efectivos, económicos y, actualmente, con un aparente mejor perfil de seguridad que en épocas previas, aunque hay que ser prudentes en su uso y seguir una estricta vigilancia de los pacientes y del líquido de diálisis.

**Palabras clave:** Aluminio. Captoreos del fósforo. Hemodiálisis. Fósforo. Ósmosis inversa..

## INTRODUCTION

Phosphate control still is one of the big challenges nephrologists must face<sup>1</sup>. There is currently a wide spectrum of compounds decreasing blood phosphate levels; however, the search for better chelators still goes on.<sup>2,3</sup> Although the use of aluminum hydroxide is not recommended anymore, it still is being used in daily clinical practice, and even more the clinical practice guidelines on bone and mineral metabolism accept the possibility of using it with limitations.<sup>4</sup>

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**Table I. Comparison before and after the introduction of aluminum hydroxide in treated patients (n = 41)**

	0 months	1 month	3 months	6 months	p
Phosphaite (mg/dl)	6.8 ± 1.2	4.8 ± 1.0	4.9 ± 1.0	4.9 ± 1.0	< 0.0001
Calcium (mg/dl)	9.2 ± 0.4	8.7 ± 0.6	8.8 ± 0.7	8.6 ± 0.5	< 0.05
Sevelamer 800 mg (Num. tablets/day)	10.4 ± 4.2	8.0 ± 3.8	8.1 ± 3.5	7.9 ± 3.7	< 0.0001
Calcium acetate 500 mg (Num. tablets/day)	4.6 ± 4.0	3.1 ± 3.3	3.0 ± 3.4	3.1 ± 3.2	< 0.0001

The toxicity from aluminum was a serious problem in hemodialysis units.<sup>5</sup> The first time that aluminum was noticed to be toxic in hemodialysis patients was in 1976,<sup>6</sup> and this metal has been implicated in dementia and dialysis-induced encephalopathy,<sup>7</sup> microcytic anemia without iron deficiency,<sup>8,9</sup> osteomalacia,<sup>10</sup> and it has been considered responsible for a big number of fractures in dialysis patients.<sup>11</sup>

Almost all bibliographical references on this topic date from the 1970s-1980s, an era during which aluminum-based chelators were the only one available and the quality standards for treated water were very much weaker than the ones currently existing.<sup>12-15</sup> Later on massive intoxications have occasionally been reported manifested as the fulminating form of aluminum-induced encephalopathy, secondary to accidents related with the water of hemodialysis.<sup>16</sup>

The aim of this study is to analyze the impact that prolonged therapy with low doses of aluminum chelators has had on a population of patients submitted to dialysis in a unit with double system of reverse osmosis and aluminum levels in the dialysis fluid lower than 2 micrograms/Liter.

## MATERIAL AND METHODS

We have studied 295 hemodialysis patients receiving dialysis at our Unit from January of 2005 to November of 2007. Forty-one patients received aluminum-based chelators during this period. The criteria for using aluminum-based chelators were the following: poor phosphate control and/or intolerance or adverse effects with other chelators such as sevelamer or calcium-based chelators. The aim was to maintain phosphate serum levels < 5 mg/dL.

We monthly measured the levels of phosphate, calcium, hemoglobin, and mean corpuscular volume (MCV), as well as the doses of erythropoiesis-stimulating agents. PTH and ferritin levels were measured bimonthly and serum aluminum levels every three months.

Before February of 2001, the water treatment plant only had one reverse osmosis system. After that date, a double system of reverse osmosis was installed. The determination of aluminum levels in the hemodialysis fluid was carried out every month before and after the implementation of that system.

## Studied variables

The following variables were compared in the patients treated with aluminum-based before starting the treatment, at 3, and at 6 months:

1. Doses of other chelators: sevelamer, calcium-based chelators.
2. Cost of each treatment.
3. Parameters of osteodystrophy: phosphate, calcium, PTH.
4. Parameters of anemia: Hemoglobin, doses of erythropoiesis-stimulating agents, MCV, and erythropoietin resistance index (ERI).
5. Serum aluminum levels.

We compared serum aluminum levels between the groups of patients receiving and not receiving aluminum hydroxide during the study period.

We compared the conductivity and aluminum level in the dialysis fluid, and serum aluminum level in patients starting on hemodialysis before and after the implementation of the double system of reverse osmosis at our Unit.

## Statistical analysis

The statistical analysis of the data was done by means of basic descriptive statistics. The results are expressed as mean ± standard deviation. The adjustment of the variables to a normal distribution was done by the Kolmogorov-Smirnov test. The differences between the groups were analyzed by the Student's t test. The association between numerical variables was established by the Pearson's correlation coefficient. A p value < 0.05 was considered to be statistically significant.

## RESULTS

From January of 2005 to November of 2007, 295 patients (62% males) received dialysis at our Unit. The mean age was 65.7 ± 15.1 years and the mean time on hemodialysis was 66.6 ± 85.7 months. Forty-one patients (13.8% of the population studied) were treated with aluminum-based chelators for controlling phosphate levels. The mean treatment time was 17.8 ± 14.6 months. The mean dose used of aluminum hydroxide (Pepsamar<sup>®</sup> 233 mg) was 3.9 ± 2.29 tablets/day, which represents a total average dose of 463 grams of aluminum received during the study period.

Table I shows the results obtained before, at 3, and 6 months of introducing therapy with aluminum hydroxide with regards to phosphate control and the use of other chelators.

Treatment with aluminum hydroxide represented a mean cost of 2.34 euros/patient/month (Pepsamar 233 mg<sup>®</sup>: 0.02 euros per tablet), as compared with 220.8 euros/patient/month for sevelamer (Renagel 800 mg<sup>®</sup>: 0.92 euros per tablet) and 6.57 euros/patient/month for calcium-based chelators (Royen<sup>®</sup>

**Table II. Indirect analysis of the potential toxicity of aluminum hydroxide in treated patients (n = 41)**

	0 months	3 months	6 months	p
Serum aluminum (mcg/l)	6.8 ± 5.03	13.8 ± 6.9	13.7 ± 7.6	< 0.0001
PTH (pg/ml)	497.9 ± 472.5	417.7 ± 263	410.2 ± 261	0.56
MCV (fl)	97.2 ± 5.3	96.1 ± 5.7	95.8 ± 6.3	0.11
Hb (g/dl)	12.1 ± 0.9	12.2 ± 1.2	12.5 ± 0.8	< 0.01
EPO dose (U/kg/semana)	196.1 ± 146.9	179.6 ± 120.2	145.4 ± 112.2	< 0.01
Resistance to EPO	16.2 ± 9.1	14.7 ± 9.2	11.6 ± 8.9*	< 0.05

\* P for the comparison between 6 months and 0 months.

500 mg; 0.07 euros per tablet). The whole cost for chelators decreased by 69.8 euros/month after introducing Pepsamar®, with a better phosphate control. After treatment with aluminum hydroxide, the percentage of patients with phosphate levels < 5 mg/dL went up from 4.9 % to 73.2% in the treated group.

Table II shows the indirect analysis of the potential toxicity from aluminum hydroxide. Five patients (12.1%) reached aluminum levels > 20 micrograms/L, and in no case this value reached 40 micrograms/L.

The average serum aluminum levels during the study period were significantly higher in patients receiving aluminum-based chelators (11.6 ± 6 mcg/L) than in the group not treated (8.7 ± 4.8 mcg/L) (p < 0.01).

In February of 2001, a serial double system of reverse osmosis was installed at our Unit. The conductivity of the treated water, aluminum in the dialysis fluid, and mean serum aluminum remarkably decreased from that date (table III).

The serum aluminum levels were significantly higher in the group of patients starting hemodialysis before the implementation, in 2001, of the double system of reverse osmosis for treating the water (N = 77) (13.06 ± 7.13) as compared with those in patients incorporating to the Unit after that date (N = 189) (8.54 ± 6.07) (p < 0.0001).

The serum aluminum levels at the end of the study in the treated patients were significantly correlated with the time on aluminum hydroxide therapy (r: 0.41; p < 0.01) and with

serum aluminum values before receiving the treatment (r: 0.58; p < 0.0001).

### DISCUSSION

The main findings from our study are the following:

1. The association of low doses of aluminum-based phosphate chelators allowed for a better phosphate control, with a reduction in the dose of other drugs.
2. Management of hyperphosphatemia with aluminum hydroxide is a more cost-effective therapy than using other chelators: a better outcome is achieved at a lower cost.
3. Serum aluminum levels increased after aluminum hydroxide therapy and remained steady at an average level of about 13 micrograms/L throughout the whole study period. We did not observe indirect signs of toxicity on MCV, hemoglobin, or PTH, and we did not observe a decrease of the ERI.
4. Mean blood aluminum levels decreased after the implementation of the double system of reverse osmosis, together with a decreased in the conductivity of the hemodialysis water and aluminum levels in the dialysis fluid < 0.002 micrograms/L. Besides, serum aluminum levels in the patients incorporating to the Unit after the change in the water treatment plant were significantly lower than those in patients incorporating to the Unit before that date.

**Table III. Evolution of annual measurements of conductivity and aluminum levels in the sera and the dialysis fluid from 1998 to 2007 (\* p < 0.0001 as compared to the years before 2001)**

Year	Conductivity (mS/cm)	Aluminum HD fluid (mcg/l)	Serum aluminum (mcg/l)
1998	34.9 ± 9.1	< 5	36.0 ± 19.1
1999	48.9 ± 9.2	< 5	27.7 ± 15.5
2000	39.9 ± 9.3	< 5	25.7 ± 13.8
2001	3.4 ± 0.2*	< 2*	15.4 ± 14.0*
2002	2.2 ± 0.3*	< 2*	19.2 ± 13.8*
2003	2.4 ± 0.2*	< 2*	13.1 ± 11.4*
2004	2.1 ± 0.4*	< 2*	11.0 ± 9.8*
2005	1.8 ± 0.2*	< 2*	9.6 ± 8.4*
2006	2.3 ± 0.1*	< 2*	11.0 ± 10.2*
2007	2.2 ± 0.2*	< 2*	9.4 ± 6.6*

Aluminum salts were the first phosphate chelators commercially available, more than 30 years ago. However, despite their high potency binding to phosphate, they have been blamed for promoting a high number of complications derived from the accumulation of aluminum in different tissues.<sup>2-7</sup> The guidelines recommending a restricted use of aluminum-based chelators have been based on the experiences of toxicity from this compound.<sup>16</sup> These experiences date from the time in which aluminum hydroxide was the only phosphate chelator commercially available, which obliged to administer high doses of this agent, and the nephrology community was not as much aware of the need for having adequate water treatment systems. Thus, the aluminum source was double: enteral and parenteral.

In our study we observed that serum aluminum levels increased after the introduction of aluminum hydroxide, and that serum aluminum levels in the treated group were significantly higher than those in the group not receiving aluminum. However, only 5 patients (12.1%) reached an aluminum level > 20 micrograms/L, a value considered by the K-DOQI guidelines as the maximum permitted value.<sup>16</sup> The mean treatment time was 17 months, higher than that recommended by the K-DOQI guidelines (3 months),<sup>16</sup> without observing a significant increase in serum aluminum levels through time; and without observing indirect signs of toxicity on the bone or anemia, hemoglobin levels, mean corpuscular volume, or PTH in our patients.

One limitation from our study is that aluminum overload has been measured indirectly through regular determination of serum aluminum, and we have not used bone biopsies or encephalograms. During several years, validation strategies have been developed allowing inferring, although not 100% sure, an aluminum-toxicity risk depending on the different aluminum levels. In fact, it has been described that a value of serum aluminum of 60 micrograms/L has a 73% predictive value for the diagnosis of aluminum-related bone disease.<sup>17</sup> It is surprising how the serum aluminum level in the patients treated with aluminum-based chelators is very much lower than this value, which would us think that tissue toxicity may be minimal or virtually inexistent. However, it would be interesting to carry out a study including bone biopsies in these patients in order to determine the exact repercussion that this therapy has on the bone under these circumstances. In a work published by Smith and coworkers [18], 50% of a sample of 97 patients on renal replacement therapy showed aluminum deposits in the bone biopsy; however, these patients had been exposed to very much higher aluminum doses both from the hemodialysis water (mean of 2.35 micrograms/L after reverse osmosis, and previously of 342 micrograms/L *vs* < 0.002 micrograms/L in our study), and from orally administered aluminum hydroxide (mean of 5.93 grams/day *vs* 0.98 grams/day in our patients). The aluminum cumulative dose from orally administered aluminum was also higher in the study by Smith, even in those patients without aluminum toxicity (2.59 kg) as compared to our group (0.463 kg). These figures are similar to those described in other works that also show aluminum in bone biopsy, and in all of them the serum aluminum values are considerably higher (> 60 micrograms/L) than those in our study.<sup>19,20</sup>

An important consideration is to avoid aluminum hydroxide in those groups of patients with a greater risk of aluminum overload such as children, diabetics, parathyroidectomized, transplanted patients returning to dialysis, individuals with iron deficiency, particularly those under erythropoietin therapy,<sup>21</sup> and those receiving therapy with citrate,<sup>22</sup> since they have increased aluminum absorption. Higher serum aluminum levels have been described in patients with low serum ferritin levels and/or transferrin saturation index, likely as a result of increased aluminum absorption at the intestinal level and/or a higher number of aluminum receptors available on transferrin.<sup>11</sup> In our study, all treated patients had ferritin levels and transferrin saturation index > 150 mg/dL and 20%, respectively.

On the other hand, an essential issue when treating with aluminum-based chelators in hemodialysis is to assure appropriate water.<sup>10</sup> Aluminum concentrations as low as 5 micrograms/L may induce a slow accumulation of this element since this concentration is sufficient to cause a positive aluminum balance.<sup>23</sup> This is way it is recommended to keep the aluminum concentration in the dialysis fluid < 1 microgram/L.<sup>10,16</sup> In our Unit, the aluminum concentration in the dialysis fluid has always been kept at < 2 micrograms/L, which is the lowest detection level of our laboratory, and in a random sample of the dialysis fluid done by a laboratory with a higher detection level it was < 1 microgram/L.

It is interesting to see the parallel evolution that the aluminum levels in the dialysis fluid, the water conductivity, and the serum aluminum levels have followed after the implementation of the double system of reverse osmosis, similar to that found by other groups.<sup>24</sup> In fact, the aluminum levels were significantly higher in those patients receiving dialysis before the implementation of the system than in those incorporating later to the Unit ( $p < 0.0001$ ). An Italian group reported a significant decrease in the amounts of bone aluminum in spite of maintaining similar amounts of oral aluminum intake in the form of chelators, attributing this finding to the decrease in the amount of aluminum contained in the dialysis fluid, which would confirm the essential role of the parenteral source in aluminum accumulation, in hemodialysis patients.<sup>25</sup>

In Spain, the percentage of centers with an aluminum concentration in the dialysis fluid < 2 micrograms/L got increased from 1990 to 1999; and almost 70% of them had undetectable aluminum levels (< 1 microgram/L).<sup>26</sup> The double system of reverse osmosis allows obtaining these values and, in some way, it represents an additional safety mechanism to prevent possible accidents due to inappropriate aluminum intake from the water system. Water may get contaminated with aluminum when aluminum sulfate is used as a sedimentation agent for treating city water, which is a common practice in many municipalities. The amount of aluminum sulfate added to the water increases during times when there are higher amounts of particles suspended in the water, either at times of drought or of torrential raining, a practice that is usually not communicated to dialysis centers.

It has been shown that hyperphosphatemia is an important mortality risk factor in hemodialysis patients.<sup>27</sup> One of the main obstacles for a successful management of chronic renal

disease lies on the lack of adherence to the therapy with phosphate chelators. Although since the 1990s we have available new chelating agents, the reality is that the ideal treatment (powerful, cheap, and well tolerated) has yet to be defined, so that we are sometimes forced to use aluminum-based chelators. Calcium salts in the form of carbonate and acetate are effective, although the current evidence suggests that high doses may increase total calcium body load with the subsequent risk for cardiovascular and soft tissue calcification.<sup>28</sup> This is why the K-DOQI guidelines limit the amount of calcium administered as chelating agents to less than 1,500 mg/day,<sup>16</sup> which also contributes to associate different chelators to achieve the goal. Sevelamer CIH is not systemically absorbed and does not bring calcium or metals; however, its binding capacity to phosphate is lower, requiring a considerable amount of tablets and the treatment cost is very high;<sup>29</sup> in addition, it may induce metabolic acidosis.<sup>14</sup> The collateral effect observed on ERI is interesting: this parameter decreases after treatment with aluminum hydroxide. This effect is likely related to a decrease in PTH as a result of a better phosphate control, a matter that has already been described in other publications.<sup>30</sup> However, in our study we could not find a relationship between both variables (data not shown), maybe because of the small sample size or the short follow-up time.

So, for the time being, the association of several chelating agents is one of the most used therapeutic options<sup>31</sup> in order to minimize the possible adverse effects from each one of them; in this setting, aluminum-based phosphate chelators have shown to be effective, cheap, and currently with an apparent better safety profile than previously. In our experience, upon balancing the risk for sustained hyperphosphatemia and aluminum-induced bone impairment, we only use this type of phosphate chelators in those cases not achieving an adequate phosphate control with other ligands, either because of intolerance or because of a lack of adherence due to high doses required of other drugs, always in combination to other agents and never at doses higher than that described in this study. Even so, we should be cautious using them, avoiding its use in the above-mentioned risk populations, and following stringent monitoring of serum aluminum levels in the patients and the dialysis fluid.

It is likely that in the future we may have available lanthanum carbonate, a potent and selective phosphate chelator, which will be soon in the Spanish market, and with which we may increase treatment adherence since the number of tablets required to obtain a similar effect is lower. A lot of hopes are placed on this product.<sup>32</sup>

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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.