The effect of replacing aluminium hydroxide with calcium acetate/magnesium carbonate on serum phosphorus control in haemodialysis patients

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ABSTRACT

Introduction: Calcium acetate/magnesium carbonate ($MgCO_3$) is a phosphorus binder with advantages in terms of cost, safety and tolerance and it has a similar efficacy to other drugs. The objective of the study is to assess the effects of replacing aluminium hydroxide [$Al(OH_3)$] with $MgCO_3$ on phosphorus and calcium metabolism in a cohort of haemodialysis patients. **Materials and methods:** We included 21 patients with phosphorus <5mg/dl, with $Al(OH_3)$ as the only binder. The conversion to $MgCO_3$ was carried out without changing the number of pills. We recorded clinical-demographic characteristics, treatment for secondary hyperparathyroidism and laboratory parameters before conversion and every month for four months. **Results:** Phosphataemia decreased from 4.52±0.99 to 4.02±1.07mg/dl (P=.027), and there was a decrease in the calcium-phosphorus product from 40.20±10.44 to 35.16±11.06mg^2/dl^2 (P=.037). We did not observe significant changes in levels of calcium, parathyroid hormone or 25-OH-vitamin D_3. The daily number of pills prescribed was reduced from 3.33±2.29 to 2.15±2.21 (P=.020). Concomitant treatments were not altered. We observed an initial significant increase in magnesaemia from 2.21±0.24 to 2.43±0.39mg/dl (P=.001), which subsequently remained stable. We found a decrease in serum aluminium from 14.91±8.55 to 8.47±3.98µg/l (P=.004), with levels within the recommended range in all patients. **Conclusions:** $MgCO_3$ allowed good control of serum phosphorus in haemodialysis patients who were previously well controlled with $Al(OH)_3$, using fewer daily pills. There was a slight increase in serum magnesium, without short-term clinical significance. We do not know the effects of this increase in the longer term.

Keywords: Haemodialysis. Hyperphosphatemia. Phosphate binders. Magnesium carbonate. Aluminum hydroxide.

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Efecto en el control del fósforo sérico tras la sustitución de hidróxido de aluminio por acetato cálcico/carbonato magnésico en pacientes en hemodiálisis

RESUMEN

Introducción: *El acetato cálcico/carbonato magnésico ($MgCO_3$) es un quelante de fósforo con ventajas en cuanto a coste, seguridad y tolerancia, con similar eficacia a la de otros fármacos. El objetivo del estudio es evaluar los efectos sobre el metabolismo fosfocálcico al sustituir hidróxido de aluminio [$Al(OH_3)$] por $MgCO_3$ en una cohorte de pacientes en hemodiálisis.* ***Material y métodos:*** *Se incluyen 21 pacientes con fósforo < 5 mg/dl, con $Al(OH_3)$ como único quelante. La conversión a $MgCO_3$ se realizó sin variar el número de comprimidos. Se registraron características clínico-demográficas, tratamiento para hiperparatiroidismo secundario y parámetros analíticos antes de la conversión, y mensualmente durante cuatro meses.* ***Resultados:*** *La fosforemia disminuyó de 4,52 ± 0,99 a 4,02 ± 1,07 mg/dl (p = 0,027), con una reducción del producto calcio-fósforo de 40,20 ± 10,44 a 35,16 ± 11,06 mg^2/dl^2 (p = 0,037). No encontramos variaciones significativas en los niveles de calcio, hormona paratiroidea o 25-OH-vitamina D_3. El número prescrito de comprimidos diarios se redujo de 3,33 ± 2,29 a 2,15 ± 2,21 (p = 0,020). Los tratamientos concomitantes no variaron. Observamos un aumento significativo inicial de la magnesemia de 2,21 ± 0,24 a 2,43 ± 0,39 mg/dl (p = 0,001), que posteriormente se mantuvo estable. Encontramos una disminución del aluminio sérico de 14,91 ± 8,55 a 8,47 ± 3,98 µg/l (p = 0,004), con niveles en rango recomendado en todos los pacientes.* ***Conclusiones:*** *El $MgCO_3$ permite un buen control del fósforo sérico en pacientes en hemodiálisis previamente bien controlados con $Al(OH)_3$, con menos comprimidos diarios. Se produce un ligero aumento en el magnesio sérico, sin significado clínico a corto plazo. Desconocemos los efectos de este aumento a más largo plazo.*

Palabras clave: *Hemodiálisis. Hiperfosfatemia. Quelantes de fósforo. Carbonato de magnesio. Hidróxido de aluminio.*

INTRODUCTION

Cardiovascular disease is the main cause of mortality in haemodialysis patients.[1] Mineral metabolism disorders, and spe-

cifically hyperphosphataemia, are one of the factors directly involved through vascular calcification.[2-5] As such, control of hyperphosphataemia and secondary hyperparathyroidism (SHPT) is one of the cornerstones of treatment in haemodialysis patients. Dietary restriction of phosphorus and appropriate dialysis are the first steps, but they are often insufficient and the prescription of phosphate binders is usually required.

Although the ideal binder has not yet been found, there are currently various drugs that are effective in terms of their main objective. However, there are differences in their pleiotropic and adverse effects and cost, and as such, the choice of binder must be rationalised and individualised for each patient.[5-8]

Aluminium hydroxide [$Al(OH)_3$] has always been one of the most powerful binders. Its use has classically been restricted due to potential toxic effects, but there is no clear scientific evidence of these effects.[9,10] We have used it regularly in our unit and have not observed higher serum aluminium levels than those recommended or related adverse events. Nevertheless, this binder has not been manufactured in recent years for commercial reasons.

One of the therapeutic options emerging in the market is the combination of calcium acetate with magnesium carbonate ($MgCO_3$). Its advantages include a lower calcium intake than other calcium binder monotherapies and a lower cost than new non-calcium binders, with the same efficacy, as well as the potential benefits of additional magnesium intake.[11]

The objective of this study was to assess tolerance and efficacy in hyperphosphataemia control when we replaced $Al(OH)_3$ (Pepsamar®) with $MgCO_3$ (Osvaren®) in a cohort of haemodialysis patients.

MATERIAL AND METHODS

Patients

Between October and December 2012, we selected patients from our haemodialysis unit who had an adequate control of phosphataemia (serum phosphorus <5mg/dl), on treatment with $Al(OH)_3$ binder monotherapy who required continuation of this treatment. We followed the indications on dietary restriction of phosphorus rich foods regularly and without variation, in accordance with the unit's standard protocol. Twenty-one patients (66.7% male, aged 56.7±16.4 years) met the inclusion criteria. They all underwent dialysis in three four-hour weekly sessions; 6 received high-flux haemodialysis and 15 received online haemodiafiltration. Both the regimen and dialysate remained unchanged throughout the study, with there being a constant magnesium concentration of 0.5mmol/l. The dialysate calcium concentration did not change and was 1.25mmol/l in eight patients and 1.5mmol/l in the remaining 13. Patient baseline characteristics are displayed in Table 1. The conversion to $MgCO_3$ was carried out without changing the number of pills or the time at which they were taken, which were indicated during or immediately after meals. The maintenance dose was adjusted to clinical criteria in accordance with monthly serum phosphorus levels.

Variables

We recorded the patients' demographic and clinical characteristics. Before the conversion and over the following four months, we collected the data related to SHPT treatment each month, as well as laboratory parameters related to phosphorus and calcium metabolism: total and free calcium, phosphorus, 25-OH-vitamin D_3, parathyroid hormone (PTH) and serum magnesium. Serum aluminium was measured at baseline and after four months. Patients were regularly questioned about their adherence to the treatment with phosphate binders.

Statistical analysis

All statistical analyses were performed using the SPSS version 17.0 software (SPSS Inc, Chicago, IL). The vari-

Table 1. Patient baseline characteristics

Variable	Percentage (n) or mean ± standard deviation
Male	66.7% (14)
Age (years)	56.7 ± 16.4
CKD aetiology	
Diabetes mellitus	28.6% (6)
Glomerular	28.6% (6)
Unknown	14.3% (3)
Vascular	9.5% (2)
Acute renal failure	9.5% (2)
Polycystic kidney disease	4.8% (1)
Interstitial	4.8% (1)
Time on dialysis (months)	78.9 ± 118.3
Kt/V	1.89 ± 0.45
Reinfusion volume (litres)	28.42 ± 3.26
Previous PD	9.5% (2)
Previous transplantation	23.8% (5)
Diabetes mellitus	33.3% (7)
Parathyroidectomy	4.8% (1)

PD: peritoneal dialysis, CKD: chronic kidney disease.

ables were recorded as percentages or as a mean ± standard deviation. Qualitative variables were compared using McNemar's test and quantitative data were analysed using the Wilcoxon signed-rank test for related non-parametric variables. We considered relationships with a *P* value <.05 to be significant.

RESULTS

We observed a statistically significant decrease in serum phosphorus levels four months after the conversion to $MgCO_3$ (4.52±0.99 versus 4.02±1.07mg/dl, *P*=.027), and in calcium-phosphorus product levels (40.20±10.44 versus 35.16±11.06mg^2/dl^2, *P*=.037). Despite the additional intake of oral calcium, the change in serum calcium was not significant (8.85±0.65 versus 8.66±0.81mg/dl). No significant changes were observed in PTH or vitamin D levels. Changes in laboratory results throughout follow-up are summarised in Table 2.

The improvement in phosphataemia control was achieved by decreasing the number of $MgCO_3$ pills (from 3.33±2.29 to 2.15±2.21 pills per day, *P*=.020). There were no significant changes in the rest of the drugs used to treat SHPT (Table 3).

We discontinued treatment with $MgCO_3$ in six patients (30%), in five due to hypophosphataemia and in one due to digestive intolerance. We observed a significant increase in magnesaemia from the first month (2.21±0.24 versus 2.43±0.39mg/dl, *P*=.001), which remained stable for four months. We recorded just one case of hypermagnesaemia (>3mg/dl), which was suitably resolved by reducing the dose.

Likewise, we found a decrease in serum aluminium levels from 14.91±8.55 to 8.47±3.98μg/l (*P*=.004), with levels being within the recommended range (<40μg/l) in all patients.

DISCUSSION

The conversion from $Al(OH)_3$ to $MgCO_3$ allowed phosphorus to be controlled adequately in this haemodialysis patient cohort. Although we were not able to demonstrate clearly that a decrease in serum phosphorus results in reduced mortality, the obvious pathophysiological role that it plays has led to clear indications in national and international guidelines.[12]

There are currently a wide variety of binders available, all of which are effective in reducing hyperphosphataemia, but with differences in other aspects that force doctors to make a decision about which binder to prescribe.[13-15] Until recently, aluminium salts were considered the most powerful binder, with a very low cost/benefit ratio.[11] However, the potential toxicity of aluminium had restricted its use in the literature to settings with fewer economic resources.[16-18] There has even been a certain concern about aluminium intake from other drugs, both in terms of hidden intake and alongside other indications, especially antacids.[19] Improvement in the treatment of dialysis water, with the resulting lower aluminium concentration, and its low cost in this period of adjustments has challenged these limitations. Various recent studies in which no long term toxicity was observed have reopened the debate on the potential use of aluminium salts.[9,10,20,21]

In our study, we found that suppressing aluminium salt-based binders effectively decreases serum levels of this element, al-

Table 2. Change in laboratory parameters after replacing aluminium hydroxide with calcium acetate/magnesium carbonate

	Before conversion	Month 1	Month 2	Month 3	Month 4
Calcium (mg/dl)	8.85±0.65	8.87±0.41	8.72±0.42	8.90±0.54	8.66±0.81
Ionized calcium (mEq/l)	0.94±0.09	0.93±0.07	0.91±0.06	0.94±0.08	0.91±0.09
Phosphorus (mg/dl)	4.52±0.99	4.57±1.11	4.05±1.16	4.05±1.08	4.02±1.07*
Calcium x phosphorus (mg^2/dl^2)	40.20±10.44	40.76±11.11	35.38±10.55*	36.11±10.26	35.16±11.06*
PTH (ng/l)	440.52±280.15	461.81±298.22	399.8±278.1	430.8±375.27	409.70±270.24
25-OH-vitamin D3 (µg/l)	15.64±9.26	13.18±6.80	15.90±6.79	12.84±5.29	13.16±6.94
Magnesium (mg/dl)	2.21±0.24	2.43±0.39**	2.47±0.44*	2.44±0.40*	2.45±0.42*
Albumin (g/dl)	3.92±0.50	3.97±0.44	4.03±0.47	4.03±0.59	3.98±0.47
Haemoglobin (g/dl)	11.55±1.37	10.96±11.40	11.22±1.09	11.37±1.32	11.37±0.99
Aluminium (µg/l)	14.91±8.55				8.47±3.98*

Results displayed as mean ± standard deviation. Statistically significant relationships are marked with * (P<.05) and ** (P<.01) compared with the sample before the conversion.
PTH: parathyroid hormone.

Table 3. Other treatments used for phosphorus-calcium metabolism disorders

		Before conversion	Month 2	Month 4
Cholecalciferol	% (n) Mean daily dose (IU)	9.5% (2) 400±0	20% (4) 360±80	15.8% (3) 346±92
Calcitriol	% (n) Mean weekly dose (μg)	9.5% (2) 0.09±0.03	10% (2) 0.09±0.03	15.8% (3) 0.15±0.09
Paricalcitol	% (n) Mean weekly dose (μg)	4.8% (1) 0.57	5% (1) 0.57	5.3% (1) 0.57
Cinacalcet	% (n) Mean daily dose (mg)	38.1% (8) 25.98±18.91	35% (8) 29.08±18.26	42.1% (8) 27.32±17.62
Calcium intake	% (n) Mean daily dose (mg)	28.6% (6) 1750±420	30% (6) 1665±755	36.8% (7) 1570±840
Other binders		0%	0%	0%
Daily dose of $MgCO_3$ (pills)		3.33±2.29[a]	3.10±2.10	2.15±2.21
Calcium concentration in dialysate (mmol/l)		1.41±0.12	1.40±0.13	1.41±0.12

Results displayed as mean ± standard deviation. No changes were statistically significant.
aThe initial number of calcium acetate/magnesium carbonate pills was the same as the number of aluminium hydroxide pills that the patient was taking.
$MgCO_3$: calcium acetate/magnesium carbonate.

though no patient had levels higher than 40μg/l at any given time. For now and until there is more evidence on the use of aluminium salts with the current water controls, the guidelines continue to advise against them. Furthermore, the manufacture and distribution of the aluminium binder available in our setting was recently interrupted, forcing us to seek other therapeutic options.

The purpose of our study was to assess the replacement of $Al(OH)_3$ with $MgCO_3$. The first studies in this line were carried out in the nineteen eighties, in different conditions to the current situation.[22] Since then, many studies have used magnesium salts as phosphate binders.[23] Of the many drugs available, $MgCO_3$ has advantages in terms of safety and tolerance, with an efficacy that is comparable to that of other more modern binders.[24] In our study, we found a significant reduction in the number of pills, which allowed an improvement in adherence and therefore in hyperphosphataemia control.[25] It also has a lower cost than other non-calcium binders, which is important in the current situation.[8]

Another advantage of using $MgCO_3$ is the benefits of magnesium intake, an element that is increasingly important.[26] There is growing evidence of the relationship between lower levels of magnesium in the general population and the occurrence or poor control of diseases such as diabetes, high blood pressure or cardiovascular disease.[27-31] In chronic kidney disease patients, reduced levels of magnesium have been associated with greater mortality, a worsening of mineral and bone disorder and an increase in vascular calcifications.[32-35] An interventional study demonstrated delayed arterial calcification with a reduction in intima-media thickness in relation to magnesium supplements.[36] At present, there are few studies on the effects of different dialysate concentrations.[37,38] It seems that there could be certain advantages to using dialysate with a higher magnesium content, such as better haemodynamic tolerance.[39] It is not clear what levels of serum magnesium are suitable, although there seems to be an increasingly greater consensus that somewhat higher levels could be beneficial for patients on dialysis. Intervention trials, which assess the medium and long term effects of increasing magnesium, whether through oral intake or higher dialysate concentrations, are necessary.

In our study, we observed a slight increase in magnesium levels, which, as in the CALMAG study, occurred at the start of treatment and subsequently remained stable.[24] Only one case of asymptomatic hypermagnesaemia was recorded, which returned to levels below 3mg/dl after dose reduction. Likewise, we only found one case of digestive intolerance due to diarrhoea, which forced us to discontinue treatment.

Our study has various limitations: it is a non-controlled observational study, with a small patient sample and without strict control of adherence to a low phosphorus diet and binders. It is possible that due to the "study effect" patients will improve their level of adherence. Neverthe-

less, the changes observed in serum aluminium and magnesium suggest that there was at least partial adherence to treatment.

CONCLUSIONS

After the conversion from $Al(OH)_3$ to $MgCO_3$, there was adequate control of serum phosphorus and patients required a lower number of pills. We observed a slight increase in magnesaemia within the normal limits, whose long term clinical significance is as yet unknown. Prospective studies with a longer follow-up period are required for an accurate assessment of the long term effect of high levels of serum magnesium in patients on dialysis.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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