

SUBSTITUTION OF ALUMINIUM HYDROXIDE BY HIGH DOSES OF CALCIUM CARBONATE IN PATIENTS ON CHRONIC HAEMODIALYSIS: DISAPPEARANCE OF HYPERALUMINAEMIA AND EQUAL CONTROL OF HYPERPARATHYROIDISM

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Summary

Al(OH)₃ was discontinued in 26 patients on chronic haemodialysis as well as vitamin D metabolites in eight. Oral CaCO₃ was progressively increased from 4 ± 3 to 10 ± 5g/d to keep plasma PO₄ < 6.0mg/dl and P Ca < 10.5mg/dl. This treatment had to be discontinued in three cases because of diarrhoea and/or uncontrolled hyperphosphataemia. In the remaining patients the control of hyperphosphataemia and of PTH values was as good or even better. Hyperalumaemia disappeared in most patients demonstrating the role of oral Al(OH)₃ in the induction of hyperalumaemia. Because of frequent transient hypercalcaemia and of the occurrence of vascular calcification in two patients, high doses of CaCO₃ after discontinuation of Al(OH)₃ are advised only in cases of hyperalumaemia.

Introduction

Prevention of interdialytic hyperphosphataemia by phosphate binders is critical for the control of hyperparathyroidism in patients on chronic haemodialysis [1]. Aluminium hydroxide or carbonate are the most widely used phosphate binders but they may cause aluminium intoxication as aluminium may be absorbed [2] and may induce hyperalumaemia [3–6] positively correlated with the daily dose or the total previous dose of oral Al(OH)₃ [7]. In fact sporadic cases of aluminium encephalopathy [8] and of aluminium osteomalacia [9] have been reported in uraemic patients not dialysed or dialysed with aluminium free dialysate. Therefore aluminium free phosphate binders are highly desirable.

High doses of oral CaCO₃ have been shown by Clarkson [10] to increase faecal loss of phosphate, decrease plasma phosphate and Ca × PO₄ product in spite of a plasma calcium increase and increase in both calcium and phosphate balance. Therefore the decrease of plasma PO₄ may be explained by a decrease of phosphate absorption and by precipitation of calcium phosphate in the body.

The fact that the use of high doses of CaCO_3 by Curtis [11] and Meyrier [12] led to improvement of bone resorption without increase of soft tissue calcification suggests that the precipitation of calcium phosphate occurs mainly in the bone, although $\text{Al}(\text{OH})_3$ was also used in the study of Meyrier. Another reason for giving CaCO_3 in uraemic patients is that it may improve acidosis [13, 14] although this was not confirmed by Berlyne [15].

The aim of this study is to answer the questions: 1) are high doses of oral CaCO_3 alone (without $\text{Al}(\text{OH})_3$) effective in preventing hyperphosphataemia and high values of PTH and in correcting hyperaluminemia and acidosis, and 2) are they safe i.e. well tolerated, and without induction of hypercalcaemia and soft tissue calcification?

Patients and methods

Twenty-six patients (13 men, 13 women; mean age 53 years) on haemodialysis for 35 ± 15 months were selected because of the stability of their plasma concentration of calcium (P Ca) and phosphate (PO_4) and their reliability in taking prescribed drugs. They were dialysed four hours three times a week with a dialysate calcium of 6.5–7.0mg/dl and a dialysate aluminium $< 20\mu\text{g/L}$ (reverse osmosis). Initially 18 of them (group I) were receiving only CaCO_3 ($4.3 \pm 3\text{g/d}$) and $\text{Al}(\text{OH})_3$ ($4.3 \pm 3\text{g/d}$) whereas others (group II) were taking also vitamin D metabolites (25OHD_3 : 25–75 $\mu\text{g/d}$ or $1,25(\text{OH})_2\text{D}_3$: 0,125–0,250 $\mu\text{g/d}$).

$\text{Al}(\text{OH})_3$ and vitamin D metabolites were discontinued and CaCO_3 doses were progressively increased in order to keep $\text{P PO}_4 < 6.0\text{mg/dl}$ and $\text{P Ca} < 10.5\text{mg/dl}$. When these limits were exceeded the patients were excluded. When only hypercalcaemia occurred, CaCO_3 was transiently discontinued and resumed at lower doses.

The following parameters were measured for three months before and six months after $\text{Al}(\text{OH})_3$ discontinuation: pre-dialysis P Ca, P PO_4 , PHCO_3 weekly, ionised calcium and alkaline phosphatase (normal range: 50–170 IU) monthly, and at the second and third month of the control period and at the fifth and sixth month of the experimental period: plasma PTH by C terminal (GPL 500 Gueris [16], normal range 10–30ng/ml) and by N terminal assays (antibody 1–34 of Desplan [17], normal range $< 0.45\text{ng/ml}$) and plasma aluminium by flameless atomic absorption spectrophotometry (normal $24 \pm 8\mu\text{g/L}$) [18] (this parameter is available in only 17 patients for technical reason).

Results

Table I summarises the results for the 23 patients who were observed for six months. Three were rapidly excluded because of diarrhoea and uncontrolled hyperphosphataemia.

In group I ($n = 16$) there was a good initial control of P Ca, P PO_4 and of the $\text{P Ca} \times \text{PO}_4$ product with $4.3 \pm 3\text{g}$ of CaCO_3 and $4.3 \pm 2.3\text{g}$ of $\text{Al}(\text{OH})_3$. After $\text{Al}(\text{OH})_3$ discontinuation and progressive increase of CaCO_3 to $9 \pm 6\text{g/d}$, there was still a good control of P Ca and P PO_4 whereas there was no change in ionised calcium, bicarbonate, alkaline phosphatase and PTH values (either C or N terminal

TABLE I

	Patients without Vit D (16)		Patients with Vit D (7)	
	Before mean \pm SEM	6 months mean \pm SEM	Before mean \pm SEM	6 months mean \pm SEM
CaCO ₃ g/d	4 \pm 1	10 \pm 1	6 \pm 1	12 \pm 2
Al(OH) ₃ g/d	4 \pm 1	0	5 \pm 1	0
Ca mg/dl	9.3 \pm 1.5	9.4 \pm 2	9.3 \pm 1	9.3 \pm 1
PO ₄ mg/dl	4.9 \pm 0.3	4.8 \pm 0.3	6.0 \pm 0.7	5.2 \pm 0.3*
HCO ₃ mEq/L	20 \pm 1	20 \pm 2	19 \pm 2	19 \pm 1
Alk Phos UI/L†	144 \pm 20	142 \pm 20	122 \pm 13	117.5 \pm 15
PTH-COOH ng/ml‡	392 \pm 60	360 \pm 50	373 \pm 65	294 \pm 60
PTH-NH ₂ ng/ml§	0.21 \pm 0.05	0.18 \pm 0.05	0.23 \pm 0.08	0.37 \pm 0.15
Al ng/ml	60 \pm 10	30 \pm 5**	50 \pm 7	38 \pm 7

p significance of the change: * < 0.02; ** < 0.005

† normal range: 50–170 IU

‡ normal range: 10–30; in primary HPT: 30–180ng/ml

§ normal range: 0–0.45ng/ml

PTH). However there was a significant decrease in plasma aluminium ($p < 0.005$).

In group II ($n = 7$) the initial control of P PO₄ was poor in spite of 6 \pm 5g of CaCO₃ and 5 \pm 4g of Al(OH)₃. With high doses of CaCO₃ alone (14 \pm 5g) there was a better control of P PO₄ and of P PO₄ \times Ca product ($p < 0.02$) whereas there was no change in P Ca, ionised calcium, bicarbonate, alkaline phosphatase, PTH and aluminium.

When individual variations of aluminium are considered (in the 17 patients with available measurements) it can be seen that before Al(OH)₃ discontinuation, plasma aluminium was normal ($< 40\mu\text{g/L}$) in only seven, moderately increased (40–100 $\mu\text{g/L}$) in nine and very high (> 100) in one, whereas after six months of Al(OH)₃ discontinuation, it was normal in 15 and moderately increased in only two.

Side effects

Besides diarrhoea and uncontrolled hyperphosphataemia which led to the exclusion of three patients, we observed moderate hypercalcaemia ($> 10.5\text{mg/dl}$) in nine patients (2–14 episodes), and frank hypercalcaemia ($> 11.0\text{mg/dl}$) in seven (1–8 episodes). Finally vascular calcification increased in one patient and occurred for the first time in another: both patients had poor control of their P PO₄ \times Ca product.

Discussion and conclusions

High doses of oral CaCO₃ (5–20g/d) alone are able to prevent interdialytic hyperphosphataemia as effectively as Al(OH)₃ in most patients on chronic haemo-

dialysis (23/26) without inducing permanent hypercalcaemia. Frequent hypercalcaemic episodes can however occur leading to frequent adjustments of the dose of CaCO_3 and requiring a close monitoring of P Ca and P PO_4 . As reflected by normal N terminal PTH values and normal alkaline phosphatase, hyperparathyroidism of our patients was well controlled before and after $\text{Al}(\text{OH})_3$.

In our haemodialysis patients, higher doses of CaCO_3 did not significantly increase plasma bicarbonate which remained around 20mEq/L. Our data are different from those of Makoff and Popovtzer [13, 14] in uraemic patients not yet on dialysis, but are in agreement with those of Berlyne [15] made on uraemic patients also not yet on dialysis but with more severe renal failure. This suggests that CaCO_3 is relatively poorly absorbed.

Discontinuation of $\text{Al}(\text{OH})_3$ leads to normalisation of the hyperaluminiaemia observed in our patients in spite of the fact that treatment of the water by reverse osmosis maintained dialysate aluminium below 20 $\mu\text{g}/\text{L}$. This demonstrates the role of oral administration of $\text{Al}(\text{OH})_3$ in inducing this hyperaluminiaemia.

Because of the necessity of close monitoring of P PO_4 and P Ca and of the possible occurrence of vascular calcification, we think that high doses CaCO_3 (> 5g/d) are advised only in patients with hyperaluminiaemia. A safer and a more reliable aluminium free phosphate binder remains to be found.

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