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Either calcium carbonate or sevelamer decrease oxalate urinary excretion in chronic renal failure patients

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SUMMARY

The rate of oxalate absorbed from intestine is highly influenced by calcium intake in healthy subjects. It is unknown whether commonly used phosphate binders modify intestinal absorption and renal excretion of oxalate in chronic kidney disease (CKD) patients. This study aims to determine if calcium carbonate or sevelamer influences on urinary oxalate excretion. Twenty patients with CKD (stage 4 and 5 pre-dialysis) were included. Two treatment (1.500 mg of calcium carbonate or 2.400 mg of sevelamer), two-period (21 days each), crossover study with balanced assignment of the order of administration, and two washout periods were the main characteristics of this study design. Laboratory analyses in each phase included: serum creatinine, calcium, phosphorus, bicarbonate, total cholesterol, and 24 h urinary excretion of oxalate, creatinine, and urea. Creatinine clearance, protein catabolic rate (PNNA), total urinary oxalate excretion, and urinary oxalate / creatinine ratio were determined. Seventeen patients completed both treatment sequences. Total urinary oxalate excretion and urinary oxalate / creatinine ratios decreased significantly with respect to washout periods either after sevelamer or calcium carbonate treatment. The decrease in urinary oxalate excretion was greater after calcium carbonate (41.2 ± 17.4%) than after sevelamer treatment (30.4 ± 23.8%). There were not significant changes in renal function or PNNA values throughout the study periods. In conclusion, either calcium carbonate or sevelamer significantly reduces urinary oxalate excretion in CKD patients. Further studies will be needed to ascertain whether the type of phosphate binder influences on the accumulation of oxalate in CKD patients.

Key words: ***Calcium carbonate. Chronic renal failure. Oxalate.***

CARBONATO CÁLCICO O SEVELAMER REDUCEN LA EXCRECIÓN URINARIA DE OXALATO EN PACIENTES CON INSUFICIENCIA RENAL AVANZADA

RESUMEN

El ácido oxálico (Ox) es una reconocida tóxina urémica. La cantidad de calcio en la dieta influye en la absorción intestinal de Ox en los sujetos sanos. Se des-

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conoce si los quelantes de fósforo que contienen calcio o los nuevos quelantes sin calcio modifican la absorción o excreción de Ox en la enfermedad renal crónica (ERC). El objetivo de este estudio fue determinar si el carbonato cálcico (CC) o el sevelamer (S) modifican la excreción urinaria de oxalato en pacientes con ERC. Se incluyeron 20 pacientes con ERC estadios 4-5 pre-diálisis sin historia previa de litiasis o enfermedades digestivas. Tras un periodo de lavado sin quelantes se asignó a cada mitad del grupo la administración de CC 1.500 mg o S 2.400 mg durante 21 días. Tras otro nuevo periodo de lavado (15 días), cada paciente recibió el tratamiento contrario durante otros 21 días. En cada fase del estudio se determinaron los siguientes parámetros séricos: creatinina, calcio, fósforo, bicarbonato, colesterol total. En orina recogida durante 24 horas se midió Ox, creatinina y urea, determinando la excreción total de oxalato, cociente Ox/creatinina, aclaramiento creatinina y tasa de catabolismo proteico. Diecisiete pacientes completaron el estudio. La administración tanto de CC como de S redujeron significativamente la excreción total de Ox y el cociente Ox / creatinina con respecto a las concentraciones en fases de lavado. La reducción de oxalato en orina fue mayor tras CC (41,2 ± 17,4%) que tras S (30,4 ± 23,8%), aunque estas diferencias entre quelantes no fueron estadísticamente significativas. El resto de los cambios bioquímicos observados fueron los esperables para cada uno de estos quelantes, sin que se observaran diferencias significativas ni en la función renal ni en la tasa de catabolismo proteico. En conclusión, tanto el CC como el S reducen la excreción urinaria de Ox en pacientes con ERC. Estos cambios son probablemente el reflejo de una menor absorción intestinal de Ox. El tipo de quelante de fósforo podría influir en la cantidad de Ox acumulado a lo largo de la evolución de la ERC.

Palabras clave: ***Carbonato cálcico. Insuficiencia renal crónica. Oxalato. Sevelamer.***

INTRODUCTION

Oxalate is normally excreted through the kidney.[1] Serum oxalate levels increase in chronic renal failure (CRF) and are above normal values in most of the patients with advanced CRF.[2-4]

In CRF not due to primary hyperoxaluria, the rate of oxalate production is low although there is chronic accumulation due to the lack of clearance through the kidney; this condition may lead to supersaturation and tissue deposition.[5,6] This oxalate accumulation may cause several side effects in CRF patients.[6-15]

One of the main oxalate sources in patients without primary hyperoxaluria is intestinal absorption.[4] The rate of oxalate intestinal absorption is highly affected by calcium intake.[16,17] Calcium salts have been used for decades as phosphorus chelating agents in CRF patients, and their potential impact on oxalate intestinal absorption has never been studied

Sevelamer hydrochloride is a new phosphorus chelating agent not containing aluminum or calcium, and which use is increasing.[18] Besides its phosphorus chelating effects, this resin also binds biliary acids, and effect that has been related with its good lipid profile.[19] However, its capacity to change oxalate intestinal absorption is unknown.

The main questions that we try to analyze in this study are: Do phosphorus chelating agents have an impact on oxalate urinary excretion in CRF patients? Is there any difference in oxalate urinary excretion depending on whether calcium carbonate or sevelamer are administered?

MATERIAL AND METHODS

Twenty patients (12 males) with advanced renal failure (stages 4 or 5 pre-dialysis) were studied. Mean age was 54 ± 17 years. Inclusion criteria were: age > 18 years; follow-up at the pre-dialysis clinic for at least 6 months; stable clinical condition; no history of renal stones or gastrointestinal diseases; adherence to prescribed therapies; and informed consent to participate in the study after detailed information.

The etiology of renal failure was: unknown (6 patients), chronic glomerulonephritis (8 patients),

chronic interstitial nephritis (5 patients), and ischemic nephropathy (1 patient).

Most of the patients were treated with angiotensin converting enzyme inhibitors, statins, and phosphorus chelating agents. At the time of the study, no patient was on vitamin D, B or C therapy. With the exception of changes in phosphorus chelating agents, no other change was done during these patients treatment for the time the study lasted.

DESIGN AND STUDY PARAMETERS

The main design characteristics of this study were: crossover study with two periods and two treatments; balanced allocation to order of therapy administration; two washout periods (Figure 1).

Patients were asked to discontinue their therapy with phosphorus chelating agents for 15 days (phase L1). After this period, the following plasma laboratory determinations were done: urea, creatinine, uric acid, total cholesterol, calcium corrected to albumin, phosphorus (Hitachi 747-200, Roche Diagnostics, Germany), bicarbonate in venous blood (IL-1306 gas analyzer, Instrumental Laboratory, Milan, Italy) and PTH (IRMA, Nicholls Institute, USA). creatinine clearance was calculated by 24-hour urine collection and the results were corrected for a standard body surface area of 1.73 m^2. With 24-h urine collection, we also determined total urea excretion and urea generation rate, which were used to calculate the protein catabolism rate according to the combine formulas of Cottini *et al.* and Maronni *et al.*, following Bergström *et al.* description.[20] Oxalate levels were measured in a 24-h urine sample by the UV enzymatic method (Boehringer Mannheim R-Biopharm, Germany). The results are expressed as total oxalate urinary excretion (mg/24 h), or as the ratio of oxalate urinary excretion (mg) and urinary creatinine excretion (g).

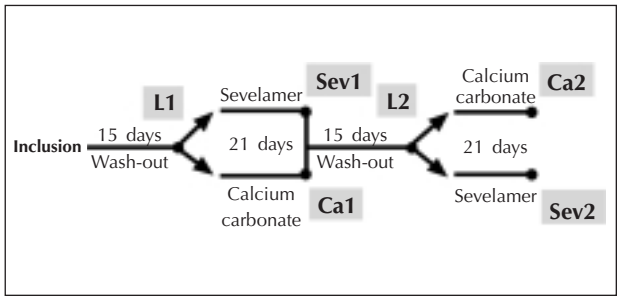

Fig. 1.—Study design. L1 and L2 (wash-out period), S (sevelamer therapy), Ca (calcium carbonate therapy).

By using a balanced allocation, half of the patients started therapy with calcium carbonate (1500 mg/day; 3 tablets of 500 mg) and the other half with sevelamer (2400 mg/day; 3 tablets of 800 mg). These doses correspond to the initial chelating therapy that is usually prescribed to pre-dialysis patients at our Unit. After being 21 days on this regimen (phases Ca1 or Sev1), the same full laboratory work-up was repeated but PTH determination. Then, phosphorus chelating agents were discontinued for another 15-days period and laboratory work-up was repeated (phase L2). Finally, calcium carbonate or sevelamer were prescribed in a crossover manner (phase Ca2 ó Sev2) and laboratory work-up was repeated after 21 days.

Patients were asked to moderate their intake of oxalate-rich foods during the study. In order to compensate for the known effects of sevelamer on acid-base balance, sodium bicarbonate, 1,5 g/day, was prescribed for the time patients were on this chelating agent.

Treatment adherence was controlled at each study period by personal interview and by observing the biochemical changes expected with regular use of each one of these medications (cholesterol, bicarbonate, calcium, etc).

STATISTICAL ANALYSIS

The study sample size was estimated by assuming an average oxalate urinary excretion of 35 ± 10 mg (values observed in pilot samples). For a type I error of 0.05, a type II error of 5%, and an expected loss to follow-up of 20%, the number of patients to be included to detect a significant difference of 25-30% in oxalate urinary excretion ought to be 20.

Paired comparisons of the means of the studies parameters before and after chelating therapies were analyzed by the student's t test.

Although this study was designed in order to avoid the carry-over effect of previous therapies by including two washout periods, as well as the potential confounding effect by the order of administration, the progression of chronic renal failure throughout the study period could have interfered in the results. In order to analyze this potential interference, comparisons between the main study variables were done at each study period.

The differences between the values of study variables of the washout period and the phosphorus chelation period were also expressed as percentages. Paired comparisons of these percentage changes were analyzed by the student's t test or the Wilcoxon's test.

The variables analyzed are presented as mean and standard deviation, with a p value < 0.05 considered as being statistically significant.

RESULTS

Seventeen patients completed both treatment sequences with chelating agents. Three patients withdrew from the study for the following reasons: one voluntarily quitted, another due to sevelamer intolerance (diarrhea), and a third one due to prolonged hospitalization secondary to heart failure.

Table I shows the study parameters after each washout period and treatment. No significant changes were observed in renal function or in protein catabolism rate throughout the study periods. Expected changes in serum levels of phosphorus, calcium, bicarbonate, and total cholesterol attributable to sevelamer or calcium carbonate therapy were observed. Uric acid level decreased significantly only after sevelamer treatment.

Oxalate urinary excretion, as well as the ratio oxalate/urine creatinine significantly decreased with both sevelamer and calcium carbonate. Only three patients showed total oxalate urinary excretion > 45 mg/24 h during the washout periods, although none of them reached higher levels after being treated with phosphorus chelating agents.

Figure 2 shows mean oxalate excretions and oxalate/creatinine ratios for each study arm and at each study period.

Percentage changes in the main study parameters as compared to the values during the washout periods are shown in Figure 3. The decrease in oxalate urinary excretion was 41.2 ± 17.4% following calcium carbonate therapy and 30.4 ± 23.8% after sevelamer. This difference between both chelating agents was not significant.

DISCUSSION

This study results show that both calcium carbonate and sevelamer decrease oxalate urinary excretion in chronic renal failure patients. Although this study did not measure serum oxalate level or oxalate fecal excretion, it is reasonable to assume that the decrease in oxalate urinary excretion was due to lower oxalate intestinal absorption.

Oxalate accumulation is a frequent finding in chronic renal failure patients.[2-6] Serum oxalate levels are strongly correlated with serum creatinine levels,[2,3] and in end-stage renal failure patients sometime serum oxalate levels exceed critical levels above which this substance precipitates and deposits in tissues.[2,5-7] Although extrarenal deposition of oxalate is an infrequent finding in autopsies of CRF patients without primary hyperoxaluria,[7] chronic oxalate accumulation has been implicated in endothelial dysfunction,[8] bone reabsorption,[9,10] vascular calcifications,[11] lithiasis,[1] arthritis,[12] proximal tubular cells damage,[13] and depositions in transplanted kidneys with a negative impact on survival.[14,15]

In healthy individuals, a calcium-rich diet reduced oxalate intestinal absorption and thus its urinary excretion.[17] For the last two decades, calcium salts have been preferentially used as phosphorus chelating agents in CRF patients. However, we are not aware of any study having analyzed the potential role of calcium salts in oxalate absorption or accumulation in CRF patients.

Total or partial substitution of calcium salts by the novel calcium- and aluminum-free chelating agents is an increasingly common practice in CRF. A hypothetical side effect of this reduction in calcium intake could be increased oxalate intestinal absorption, a possibility that has not been studied so far.

The results form the present study confirm the expected role of calcium in reducing urinary oxalate

Table I. Studied parameters after each washout and treatment period

	Wash-out	Sevelamer	Wash-out	Calcium carbonate
Serum creatinine, mg/dL	4.48 ± 0.99	4.47 ± 1.03	4.59 ± 1.10	4.74 ± 1.10
Creatinine clearance, mL/min/1.73 m^2	17.36 ± 4.31	17.79 ± 3.01	16.99 ± 3.61	17.28 ± 3.43
Protein catabolism rate, g/Kg/day	1.02 ± 0.22	0.95 ± 0.21	0.97 ± 0.23	0.98 ± 0.25
Serum uric acid, mg/dL	6.73 ± 1.69	6.29 ± 1.73[a]	6.66 ± 1.43	6.51 ± 1.76
Serum calcium, mg/dL	9.37 ± 0.64	9.43 ± 0.61	9.08 ± 0.46	9.61 ± 0.58[b]
Serum phosphorus, mg/dL	4.84 ± 0.96	4.48 ± 0.79[c]	5.12 ± 1.07	4.51 ± 0.63[d]
Serum bicarbonate, mmol/L	21.53 ± 1.99	21.15 ± 1.94	21.50 ± 1.94	23.25 ± 2.19[b]
Serum cholesterol, mg/dL	197 ± 45	154 ± 31[b]	180 ± 41	182 ± 41
Oxalate urinary excretion, mg/24 h	33.2 ± 12.2	21.8 ± 8.6[b]	34.8 ± 11.2	21.4 ± 10.9[b]
Urine oxalate/urine creatinine, mg/g	28.5 ± 9.2	18.9 ± 6.5[b]	30.2 ± 7.6	16.7 ± 5.8[b]

Student's t test. Sevelamer or calcium carbonate vs. their corresponding washout periods.
[a]p = 0.02, [b]p < 0.0001, [c]p = 0.06, [d]p = 0.003.

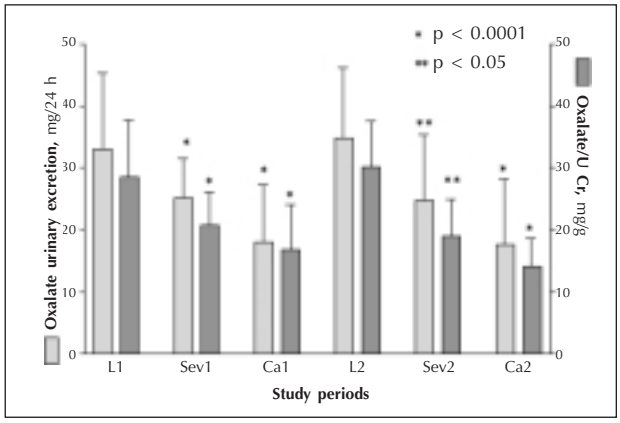

*Fig. 2.—Oxalate urinary excretion and urine oxalate/urine creatinine ratio at each study phase and with each treatment. * p < 0.001 as compared to the wash-out period; ** p < 0.05.*

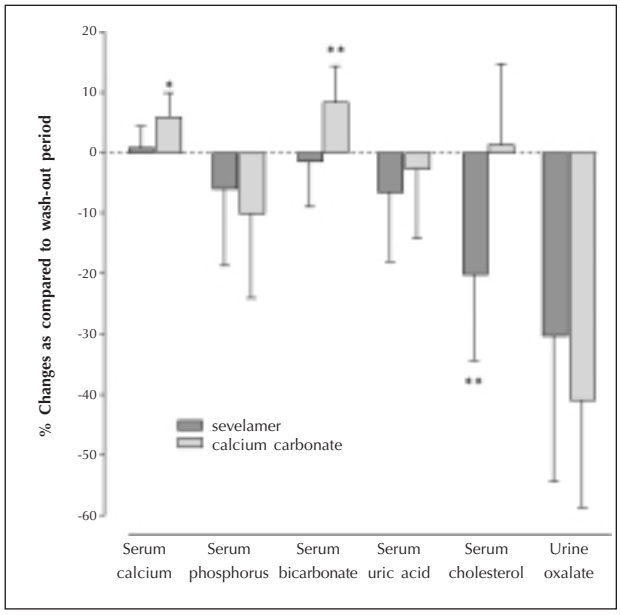

*Fig. 3.—Percentage changes of the main studied parameters as compared to values during the washout periods. * p < 0.005 sevelamer vs. calcium carbonate; ** p < 0.0001 sevelamer vs. calcium carbonate.*

(> 40%) and bring the novelty of sevelamer capacity to also decrease oxalate urinary excretion.

In the present study the mechanism by which sevelamer reduced oxalate urinary excretion was not determined. Sevelamer is a cationic hydrogel able to chelate phosphorus in the bowel.[18] Besides, this drug shares some characteristics with biliary salts chelators (cholestyramine or colestipol).[19] Biliary salts increase oxalate absorption in the large bowel.[21,22] Cholestyramine does not directly modify oxalate absorption, although it may reduce its intestinal absorption indirectly acting through chelation of biliary salts.[22] Additional studies are needed to determine whether reduction in oxalate urinary excretion showed by sevelamer is due to intrinsic chelating properties of this substance in the bowel, or to an indirect mechanism similar to that observed with other biliary salts chelators.

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