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Safety and effectiveness of nicotinic acid in the management of patients with chronic renal disease and hyperlipidemia associated to hyperphosphatemia

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SUMMARY

Objective: *To establish if the nicotinic acid in patients with chronic renal disease reduce significantly and with security the levels of lipids and serum phosphate in refractory patients to the classical management.* Design: *Observational study Place: Renal Unity RTS Ltda Caldas Santa Sofía Hospital.* Patients: *All the patients with chronic renal disease in dialysis therapy to whom the classical treatment for their hyperlipidaemia and hyperphosphatemia didn't manage a satisfactory reduce of their serum levels.* Methods: *It was identified that those patients who in the 3 previous months to the intervention hadn't presented changes in the lipids profile even though they received low fats diet and a lipid lowering therapies (statin o fibric acid derivates). It was determined in them whether they presented levels of serum phosphorus greater than 5,5 mg/dl even though having received nutritional recommendations and treatment with oral phosphate binding agents (Aluminum hydroxide, Calcium salts or Sevelamer). In them it was proceeded to administrate nicotinic acid via oral at night until a doses of 1,000 milligrams was reached (preceded of 100 mgs of acetylsalicylic acid 1 hour before) during a period of 8 months, observing its therapeutical effectivity and security profile to improve the lipids profile and reduce the serum phosphorus.* Results: *9 patients complied with the requirements, average time in dialysis 34 months, 3 in hemodialysis and 6 in peritoneal dialysis. All patients started with 500 mgs and 3 months later correctly tolerated the dose of 1,000 mgs. Between the evaluated variables, the most important changes were: the phosphorus reduced reaching a significant value at eight months: initial 6.46 ± 0.53, four months 4.37 ± 0.63 (p > 0.05) and eight months 3.94 ± 0.76 (p < 0.01); the product Ca x P obtained important reductions at four and eight months; the total Cholesterol and Triglyceride was significant reduced at all periods, not being so for the LDL, although the HDL elevated to significant values at eight months. There were no significant modifications in the LDL cholesterol, intact PTH, hemoglobin, platelet count, hepatic function tests (AST, ALT and Bilirubin), coagulation tests (TTP and TP), uric acid, glycemic control, albumin, creatinine, BUN, % transferring saturation, ferritin, folic acid and Vitamin B_{12}. No patient presented collateral or clinical effects of importance, being the adherence to the medicament 100%.* Conclusions: *The nicotinic acid is efficient, very well tolerated and economical in comparison with others drugs, which makes it ideal for the treatment of patients with hyperlipidaemia and refractory hyperphosphatemia to the classical treatments.*

Key words: *Nicotinic acid. Hyperlipidaemia. Hyperphosphatemia. Chronic renal failure.*

RESUMEN

Objetivo: **Establecer si el ácido nicotínico logra reducir significativamente y con seguridad los niveles de lípidos y fósforo sérico en pacientes refractarios al manejo clásico y con enfermedad renal crónica. *Diseño:* Estudio observacional Lugar: Unidad Renal de RTS Ltda. Sucursal Caldas Hospital Santa Sofía. *Pacientes:* Todos los pacientes con enfermedad renal crónica en terapia dialítica en quienes a pesar de recibir un tratamiento clásico para su hiperlipidemia e hiperfosforemia no lograron una reducción satisfactoria en sus niveles sericos. *Métodos:* Se identificaron aquellos pacientes quienes en los tres meses previos a la intervención habían presentado alteraciones en el perfil lipídico a pesar de recibir dieta baja en grasas y un hipolipemiante (estatina o fibrato). En ellos se determinó si presentaban cifras de fósforo sérico mayores a 5,5 mg/dL no obstante haber recibido recomendaciones nutricionales y tratamiento con quelantes de fosfato vía oral. En ellos se procedió a administrar ácido nicotínico vía oral en la noche hasta llegar a una dosis de 1.000 miligramos (precedido de 100 mg de ácido acetilsalicílico 1 hora antes) durante un periodo de 8 meses, observando su efectividad terapéutica y perfil de seguridad para mejorar el perfil lipídico y reducir el fósforo serico. *Resultados:* Nueve pacientes cumplieron con los requerimientos, tiempo promedio en diálisis 34 meses, 3 en hemodiálisis, 6 en diálisis peritoneal. Todos los pacientes iniciaron con 500 mg y a los 3 meses llegaron y toleraron bien la dosis de 1.000 mg. Entre las variables evaluadas los cambios más importantes fueron: el Fósforo (P) se redujo alcanzando su disminución un valor significativo a los 8 meses : inicial 6,46 ± 0,53, 4 meses 4,37 ± 0,63 (p > 0,05) y 8 meses 3,94 ± 0,76 (p < 0,01); el producto Ca x P obtuvo reducciones importantes a los 4 y 8 meses; la reducción en el Colesterol total y los Triglicéridos fue significativa en todos los periodos, no sien-**

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C. A. Restrepo et al. Nicotinic acid for managing hyperlipidemia in CRD

do así para la LDL, aunque la HDL se elevó a valores significativos a los 8 meses. No se presentaron modificaciones significativas en la LDL colesterol, PTH intacta, hemoglobina, conteo plaquetario, pruebas de función hepática (AST, ALT y bilirrubinas), pruebas de coagulación (TTP y TP), ácido úrico, glicemia, albúmina, creatinina, Bun, % saturación de transferrina, ferritina, ácido fólico y Vitamina B$_{12}$. Ningún paciente presento efectos secundarios clínicos de importancia, siendo la adherencia al medicamento del 100%. *Conclusiones:* El ácido nicotínico es eficiente, muy bien tolerado y de bajo costo en comparación con otros medicamentos hipofosforémicos, lo cual lo hace ideal para el tratamiento de pacientes con hiperlipidemia e hiperfosforemia refractaria a los tratamientos clásico.

Palabras clave: Ácido nicotínico. Hiperlipidemia. Hiperfosfatemia. Enfermedad renal crónica.

INTRODUCTION

Hyperphosphatemia is a common mineral disorder in chronic renal disease (CRD); phosphate retention is early detected from glomerular filtration rates (GFR) lower than 70 mL/min and is the result of kidney inability to clear through glomerular filtration the daily phosphate nutritional load, which is of around 1,000-1,800 milligrams, being mainly absorbed at the small bowel. When GFR drops below 25 mL/min the compensating mechanisms allowing for adaptation and excretion of phosphate daily load are depleted resulting in hyperphosphatemia, which is detected in 50% of hemodialysis patients.[1]

The consequences of hyperphosphatemia are the following: a- decreased serum calcium since phosphates precipitate peripherally with calcium; b- decreased renal production of the active form of vitamin D3; and c- direct stimulation of the parathyroid glands to synthesize and secrete parathormone,[1-3] these mechanisms accounting for the secondary hyperparathyroidism seen in CRD.

After recommending a low-phosphate diet, the administration of phosphate-chelating agents p.o. is the second tool to reduce serum phosphate levels; unfortunately, each one has its own drawbacks: aluminum hydroxide produces neurological impairments, osteomalacia and anemia; calcium salts increase the calcium-phosphate product precipitating in soft tissues, and both Sevelamer and lanthanum carbonate are very expensive medications.[4]

Lipid disorders are also very common in CRD, with a preponderance of triglycerides elevations in patients submitted to hemodialysis, and an increase in total cholesterol and LDL and a reduction in HDL in patients on peritoneal dialysis.[5] The hyperlipidemia-hyperphosphatemia association places the patients with CRD at an extremely high risk for cardiovascular complications with a significant decrease in their life expectancy.[6]

Nicotinic acid is an old medication mainly used to treat hyperlipidemia although it has been recently discovered to have the ability to inhibit intestinal phosphate absorption, in part by decreasing the expression of protein NaPi-2b[7] responsible of the sodium-phosphate co-transport at the bowel.[8-10] The previous observations were, therefore, the reason for starting using this drug in a group of patients meeting the characteristic of being hyperlipidemic and hyperphosphatemic and having CRD, so that a double benefit and low cost would be expected.

MATERIAL AND METHODS

During the process of monthly para-clinical follow-up of the patients regularly attending the Renal Unit of the RTS Ltda. Caldas Subsidiary at the Santa Sofía Hospital (Manizales, Caldas, Colombia) for their dialytic therapy, we recorded those patients having had lipid profile impairments within the last three months, identifying those in which lipid levels remained high (any of the following: total cholesterol > 200 mg/dL, LDL > 100 mg/dL, triglycerides > 300 mg/ dL) in spite of continuous use of statins (lovastatin) or fibrates (gemfibrozil) for the last four months (these two drugs were nerve combined). We also determined whether the patients had hyperphosphatemia (serum phosphate > 5.5 mg/dL) in spite of having received nutritional recommendations and a phosphate-chelating agent p.o. for 3 months. The latter could have been aluminum hydroxide for 4 weeks maximum, followed by sevelamer for 8 weeks at a maximal dose of 2 tablets per meal whenever the Ca x P product was > 55 or serum calcium levels > 10.2. When the product was < 55 and serum calcium < 9.5 calcium salts were used (calcium carbonate) at a maximal dose of 600 mg of elemental calcium per meal. If the patient met the criteria of having the two impairments (refractory hyperlipidemia and hyperphosphatemia) he/she was considered candidate for daily administration of nicotinic acid (Niaspan®- slow-release tablets of 500, 750 and 1,000 mg), 500 mg at night initially, and if he/she tolerated, the dose was progressively increased up to a maximal dose of 1,000 milligrams within 3 months from the start, always preceded one hour before in a protocoled way by acetyl salicylic acid. During the time the patients received nicotinic acid any other oral phosphate-chelating agent was withdrawn and we made sure they had not received vitamin D during the previous months, which is contraindicated in the presence of hyperphosphatemia; they still received oral statin or gemfibrozil, which were combined to nicotinic acid. Patients presenting liver disease, peptic ulcer, neoplasms, and gout or hyperuricemia were excluded.

The drug was administered for 8 months to each patient, recording the appearance of side effects, and monthly pre-dialysis examinations were ordered, or at 2, 3, or 4 months interval periods according to usual controls established at the nephrology unit, the parameters being determined by routinary laboratory methods. Since the impairment entailing the greatest cardiovascular risk for the patient was hyperlipidemia, and nicotinic acid has been approved to be used in hyperlipidemic patients with chronic renal disease,[5, 11] we did not asked for the patients' informed consent for administering nicotinic acid, of which we were seeking whether or not it had a beneficial effect reducing the phosphate level.

In order to obtain a urea KT/V, we used the recommendations suggested by UPTODATE 14.1 (KT/V calculator), taking into account all variables this method considers.

The statistical software used was EpiInfo, version 6.04d,

C. A. Restrepo et al. Nicotinic acid for managing hyperlipidemia in CRD

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developed by the World Health Organization (WHO). The quantitative variables were analyzed by averages and standard deviations, by using the Student's t test; the qualitative variables were analyzed by proportions and the chi-squared test.

RESULTS

Nine patients (6 women, 3 men) were included in the observational study, with mean age of 48.2 years; the cause of chronic renal disease was: hypertensive nephropathy,[2] diabetic nephropathy,[3] lupus nephropathy,[2] myeloma kidney,[1] and unknown origin;[1] the average time on dialysis was 34.7 months, 3 patients were on hemodialysis and 6 on peritoneal dialysis. All patients received at 3 months the dose of 1000 milligrams and kept on take it during all the observation period, achieving a 100% rate of treatment adherence.

We found significant modifications in the para-clinical parameters evaluated, the most important being: serum calcium (Ca) was progressively increased, and at 8 months it went up from an initial value of 9.63 ± 1.13 to 10.25 ± 0.67 ($p < 0.05$); phosphate (P) was reduced reaching a significant change at 8 months: baseline 6.46 ± 0.53, at 4 months 4.37 ± 0.63 ($p > 0.05$), and at 8 months 3.94 ± 0.76 ($p < 0.01$); the Ca x P product was importantly reduced at both 4 and 8 months; the decrease in total cholesterol and triglycerides was significant at all control moments, not being so for LDL, although the HDL levels were significantly increased at 8 months; intact PTH was not importantly changed (see table I and figs. 1, 2, and 3). There were no important modifications in hemoglobin values, white blood cells, platelet count, liver function tests (AST, ALT, total and direct bilirubin), coagulation tests (PTT and PT), uric acid, glycemia, albumin, creatinine, BUN, % transferrin saturation, ferritin, folic acid, and vitamin B12 (see table II). The average KT/V was 1.98 a no patient presented the known side effects generated by this medication: pruritus, facial flushing, diarrhea, or gouty episodes.

DISCUSSION

CRD patients are 10-100 times more likely to suffer from a cardiovascular event than the general population.[6] High serum phosphate levels have been shown to be associated with higher mortality for all causes, cardiovascular mortality, and vascular and valvular calcifications,[12-15] so that it is estimated that for each 1 mg/dL of serum phosphate increase in CRD patients, the risk for having a myocardial infarction episode increases by 35%.[16] It is then clear that reducing serum phosphate levels to the values recommended in the DOQI guidelines (< 5.5 in stage 5 CRD) is a goal that should be looked for by all nephrologists,[17] a goal we are far from reaching as it has been recently evidenced, since only 44% of all hemodialysis patients present a phosphate level within the normal range.[15]

Both low-phosphate diet and 4-hour conventional hemodialysis have failed to show to be able to achieve the suggested goals,[18] so that the use of oral phosphate-chelating agents is needed, which allow clearing this mineral through the intestinal tract.

Table I. Laboratory results in treated patients

	Month 0** Start of nicotinic acid	Month 4** Difference 0-4 months (p)		Month 8** Difference 0-8 months (p)	
Calcium (Ca)	9.63 (1.13)	9.81 (0.78)	*	10.25 (0.67)	#
Phosphate (P)	6.46 (0.53)	4.37 (0.63)	*	3.94 (0.76)	+
Ca x P product	62.44 (7.19)	42.27 (7.46)	+	40.54 (9.36)	+
Total cholesterol	283 (86.04)	243 (73.6)	+	206.44 (50.3)	+
LDL	155.56 (65.94)	142 (73.6)	*	114 (50.55)	*
HDL	45.56 (5.62)	48.67 (5.3)	*	50.22 (5.56)	#
Triglycerides	413.89 (211.44)	255 (83.67)	+	242.9 (90)	#
Intact PTH	318.22 (396.47)	322.7 (472.49)	*	334 (343)	*

*$p > 0.05$, #$p < 0.05$, +$p < 0.01$.
**Mean and standard deviation.
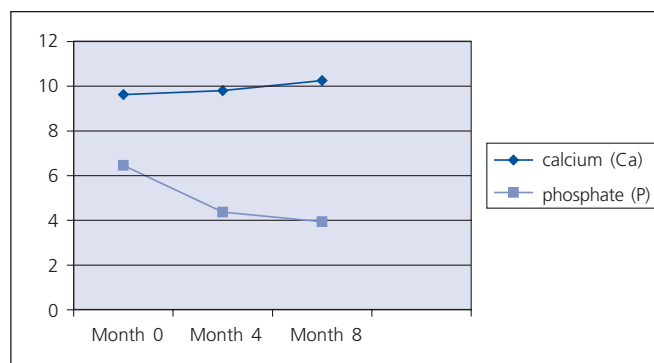
Figure 1.

Figure 2.

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C. A. *Restrepo* et al. Nicotinic acid for managing hyperlipidemia in CRD
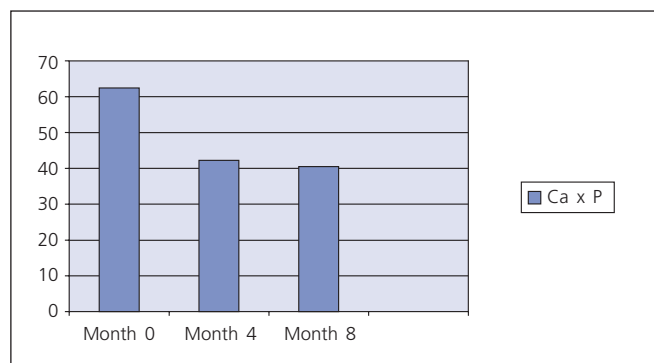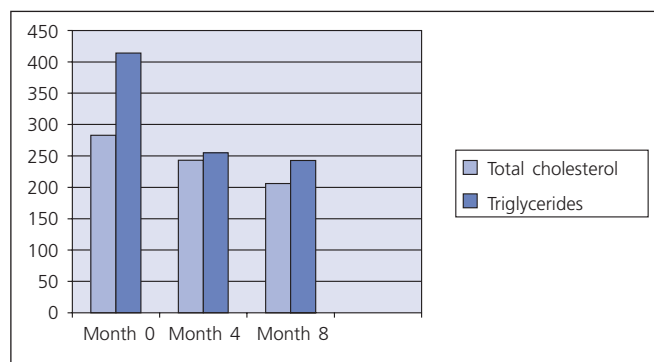
Table II. Laboratory results in treated patients

	Month 0**	Month 4**	Month 8**
Hemoglobin	11.29 (1.40)	12.74 (1.73)	11.55 (1.56)
Platelet count	237333 (74949)	227111 (85251)	238375 (65861)
Glycemia	107.8 (60.24)	92 (59.87)	108 (48.54)
Albumin	3.56 (0.61)	3.33 (0.51)	3.67 (0.68)
Alkaline phosphatase	236 (139.89)	219 (213,86)	102 (74.44)
AST	20.44 (8.75)	21.44 (9.42)	24.78 (9.03)
Uric acid	5.14 (0.91)	4.92 (1.23)	4.77 (1.18)
Ferritin	621.71 (404.57)	506.22 (457.24)	508.00 (331,07)
% transferrin saturation	29.33 (12.09)	25.88 (11.90)	32.33 (17.31)
Folic acid	6.33 (2.57)	6.03 (2.67)	9.45 (3.42)
Vitamin B$_{12}$	584.83 (337.16)	693 (277.79)	725 (304.56)

**Mean and standard deviation.

Aluminum hydroxide and calcium salts had been used for decades as chelating agents, although their marked side effects have led to limit their use to a special group of patients.[4] Lanthanum carbonate is a rare Earth element with good chelating properties, although to date there is concern about its safety profile because of the high liver accumulation it presents,[19] Sevelamer being then the first choice chelating medication nowadays. Sevelamer is a synthetic ionic interchanger,[20] which efficacy has been shown in a large number of studies.[21,22] Unfortunately, its high cost and high number of tablets the patient has to take every day until achieving control of serum phosphate levels make it difficult to be prescribed at our setting.

The ability of nicotinic acid, its active metabolite being nicotinamide and its pro-drug niceritrol, to reduce serum phosphate in CRD patients has been shown since several years ago,[23,24] and recently the efficacy of nicotinamide has been compared to that of sevelamer,[25] and that of low-dose nicotinic acid to Lanthanum carbonate,[26] both drugs achieving a very similar therapeutic efficacy, with the advantage of requiring one or two doses per day and being very cost-effective.[27] By contrast to what happens with nicotinic acid, which in our country is marketed in slow-release tablets of 500, 750, and 1,000 milligrams, nicotinamide is a magisterial preparation and although it has a good phosphate-reducing effect it has the disadvantage of presenting marked side effects,[28] as it was observed in the work by Galeano C. and coworkers, in which 1 g/day of nicotinamide achieved a significant reduction in serum phosphate at the expense of the occurrence of many side effects.[28]

The hypophosphatemic effect of nicotinic acid was discovered by chance by Shimoda and coworkers when they observed that the administration of Niceritrol to hemodialysis patients with HDL-hypocholesterolemia significantly reduced serum phosphate levels.[24] That led them to carry out a double-blind study confirming this effect as compared with placebo[29] and they later showed in experimental animals that the effect was generated by increasing fecal phosphate waste, but not urinary waste.[30] Its basic action mechanism lies on the inhibition of the activity or expression of the sodium-phosphate co-transporter protein (NaPi-2b) at the small bowel,[7,31] which activity is regulated by serum phosp-

hate levels and by active vitamin D [1,25 OH (2) vitamin D (3)].[32-34] Nicotinic acid is a group B vitamin, which is converted in the body to the dinucleotides adenosine nicotinamide (NAD) and phosphate adenosine nicotinamide (NADP), which are co-enzymes of many oxidation-reduction reactions. It has been observed that after administering nicotinamide, NAD concentrations at the renal cortex are significantly increased, then inhibiting phosphate uptake by the vesicles within the brush border of proximal tubule cells of the rat, even at conditions of low-phosphate diet; this absorption mechanism is mediated by protein NaPi-2a.[35,36] It is likely that these high concentrations are also generated at the small bowel mucosa, and thus exerting a similar effect on protein NaPi-2b inhibiting its function[31] and promoting increased fecal phosphate wasting. In our work, we observed that nicotinic acid generated a significant decrease in serum phosphate levels at 8 months, but not at 4 months. This very likely indicates that the required dose the patients should take to achieve the target effect may be of 1,000 milligrams, since at that time 100% of them were already receiving that dose.

In addition to the hypophosphatemic effect, nicotinic acid has a very notorious hypolipidemic action. This is the result of its ability to reduce VLDL and triglycerides synthesis and increase that of HDL at the liver, being able to also reduce by 10%-15% LDL and total cholesterol levels.[37-40] Its effect is generated by stimulation of the GRP109A receptor on the adipocytes, in which it exerts an inhibitory effect of hormone-sensitive lipase.[41] Total cholesterol and LDL levels were decreased in the present work, although this may be the result of the association of nicotinic acid with the hypolipidemic drug the patients had previously received and not of the isolated effect of this drug.

Intact PTH levels were not significantly changed and we have not a clear explanation of why, although it may be that the absence of changes in PTH levels would suggest that nicotinic acid might interfere with the Na-Pi co-transporter on the membrane of parathyroid cells, blocking their action and preventing that modifications in extracellular phosphate levels affect the production and secretion of parathormone.[42] A longer follow-up period and a higher number of patients are required to really obtained data with higher statistical power, although it is convenient to underline that phosphate and calcium control seems to be more important than controlling PTH, since the relationship between mortality and phosphate or calcium seems to be more consistent (or less complex) than that associated with PTH.[20] In our study, the reduction in alkaline phosphatase levels, from an average baseline value of 236 to 219 at 4 months and 102 at 8 months, suggests that nicotinic acid alters the process of bone remodeling by modifying serum phosphate levels.

The following side effects attributable to high doses of nicotinic acid used in dialysis patients have been described: diarrhea,[43] gout, headache, facial flushing, pruritus, thrombocytopenia,[23,44] hyperglycemia, increased liver enzymes and hyperuricemia, although in recent publications of studies done with slow-release preparations the occurrence of collateral effects has been the same as with placebo.[45,46] None of these clinical and analytical side effects occurred in our patients; this

C. A. Restrepo et al. Nicotinic acid for managing hyperlipidemia in CRD

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was likely due to low doses used (maximum 1 gram), and of routine administration of acetyl salicylic acid (100 mgs 1 hour before), which blocks the prostaglandin releasing effect (PGD2 and PGE2) induced by nicotinic acid through its receptor GPR109A, mainly in cutaneous immune cells.[41]

To conclude, this is the first longest work (8 months) published to date using slow-release nicotinic acid, and showing its therapeutic effectiveness to improve the lipid profile and correct refractory hyperphosphatemia, showing that this drug is safe, cheap, and easy to administer once daily, which notably increases the patient's adherence, and being until today the ideal therapy to be prescribed when hyperlipidemia e hyperphosphatemia combine to classical therapy of CRD patients.

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C. A. Restrepo et al. Nicotinic acid for managing hyperlipidemia in CRD

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