Safety and efficacy of nicotinamide in the management of hyperphosphatemia in patients on hemodialysis

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ABSTRACT

Hyperphosphatemia is an important modifiable risk factor for death and cardiovascular events in patients on hemodialysis (HD). As nicotinamide has been shown as an inhibitor of sodium–dependent phosphate co–transport in rat renal tubule and small intestine, we examined whether nicotinamide reduces hyperphosphatemia in patients undergoing HD. The study was conducted in 30 end-stage renal disease (ESRD) patients [20 (66.7%) males and 10 (33.3%) females; mean age 54 ± 14.9 years] undergoing twice/thrice weekly HD for more than 3 months. Patients on other phosphate binders were given a 2-week wash-out period. Nicotinamide 250 mg capsules were given twice daily for 25 patients with serum phosphorus greater than 5 mg/dL and thrice daily for 5 patients with serum phosphorus greater than 8 mg/dL immediately after food for 8 weeks. Serum phosphate and calcium levels were estimated every month prior to HD session, and complete blood count, blood sugar, renal profile, liver function tests were estimated at beginning and end of the study. Patients were regularly monitored for side effects. There were significant decreases in the serum phosphate (6.85 ± 1.35 mg/dL at the baseline to 5.74 ± 1.18 mg/dL at the 4th week and to 4.54 ± 0.86 mg/dL at the 8th week), the serum calcium-phosphorus product (57.8 ± 12.21 at the baseline to 48.3 ± 10.71 on 4th week and to 38.201 ± 8.21 at the 8th week), and alkaline phosphatase levels (130.23 ± 50.13 IU/L at the baseline to 116.40 ± 48.27 IU/L after 8 weeks) on treatment with nicotinamide ($P < 0.001$). Other parameters remained unchanged. Watery stools reported by seven patients resolved during the course of the therapy. Nicotinamide is safe, cheap and effective in controlling serum phosphorus, Ca × P product and alkaline phosphatase levels in patients on maintenance HD.

Key words: Hemodialysis, hyperphosphatemia, nicotinamide, phosphate, renal disease

Introduction

Hyperphosphatemia is invariable amongst patients with end-stage renal disease (ESRD), and is an important and modifiable risk factor. Patients with serum phosphorus greater than 6.5 mg/dL have a 27% higher mortality risk than those with phosphorus levels between 2.4 and 6.5 mg/dL.[1] The long–term consequences of inadequate phosphate control include secondary hyperparathyroidism, metabolic bone disease, calcific uremic arteriolopathy, and cardiovascular calcification. Progressive increases in arterial calcification are associated with greater rates of mortality.[2]

Adjusted mortality increases by 20-40% with extreme increases in inorganic phosphorus (above 4.2 mg/dL) and similar effects have been reported for calcium × phosphorus (Ca × P) product (>45.9).[1,3] An increased Ca × P product is associated with calcium–phosphate precipitations in blood vessels, myocardium, and heart valves.[4]

Inorganic phosphorus has been a categorized as a true uremic toxin.[5-7] Guidelines recommend normalization of phosphate levels in ESRD patients which is rarely achieved by extracorporeal therapy alone.[8,9]

The treatment for hyperphosphataemia in ESRD has been based on the use of oral phosphate binders taken at mealtimes. Calcium–based agents have traditionally been used as first-line therapy since they correct hypocalcemia in addition to reducing serum

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phosphate levels and are inexpensive. However, these agents may not be suitable for all patients because of dose–limiting hypercalcaemia.[10]

Aluminum hydroxide administration can lead to anaemia, osteomalacia, myopathy, and dementia and magnesium based agents causes gastrointestinal intolerance.[11]

Sevelamer was the first non-calcium, aluminum–free agent to be approved for use. Sevelamer may aggravate metabolic acidosis, gastrointestinal disturbances and also expensive; so is lanthanum.[12-16]

Nicotinamide reduces intestinal phosphate absorption by inhibiting the gastrointestinal sodium/phosphate 2b transporter (Na/Pi 2b).[17-22] Unlike niacin, it does not activate G-protein receptors specific for niacin and does not cause flushing.[23-26] However, it has dose-related gastrointestinal side effects, including diarrhea and cramping. Heartburn is a rare side effect of nicotinamide.[27] The majority of reported side effects have been reversible after discontinuation of the drug.[28,29]

For many years it has been thought that niacin raises high density lipoprotein (HDL) cholesterol and reduces triglyceride levels. Recent studies of nicotinamide therapy in patients undergoing dialysis have proved that it also increases HDL cholesterol.[30-35]

Keeping in view the need of inexpensive phosphate control, nicotinamide was studied to find out the efficacy and safety in reducing serum phosphorus in HD patients.

Materials and Methods

A prospective study was conducted in the dialysis unit of a 1700- bedded tertiary care teaching hospital, with the approval of the institutional ethics committee. The study population consisted of 30 ESRD patients aged above 18 years, undergoing twice/thrice weekly HD for over 3 months. Patients who were taking a stable dosage of phosphorus binders (calcium carbonate/calcium gluconate) for 1 month before the study and whose serum phosphorus levels were greater than 5 mg/dL after the washout period were included in the study, after obtaining their consent. Pregnant women, patients who had a history of liver disease and peptic ulcer disease and patients who were scheduled for any surgical procedures were excluded.

Study patients were made to discontinue the phosphate binders and given a 2-week washout period before administration of niacinamide. Patients whose serum phosphorus was greater than 5 mg/dL after the 2-week washout period were started on niacinamide 250 mg capsules twice daily immediately after food for 8 weeks. Patients whose serum phosphorus was greater than 8 mg/dL after the 2-week washout period were given niacinamide 250 mg capsules thrice daily immediately after food for 8 weeks, and after 8 weeks, niacinamide therapy was stopped.

Nutritional counseling was given to all HD patients to limit the intake of diet rich in phosphorous, which included- moderate protein intake (about 1.0 g/kg/day), increasing the proportion of plant–derived foods as sources of protein since their phosphorus content is less absorbed, and restricting consumption of highly processed fast and convenience foods.

Biochemical parameters were analyzed by standard clinical laboratory measures. Serum phosphorus and calcium levels where estimated once every month prior to HD session and other parameters like complete blood count, blood sugar, renal profile, and liver function tests were estimated at beginning and end of the study. Patients were regularly monitored for side effects like gastrointestinal discomfort during the study period. Comparison of serum phosphate levels at the baseline, at the end of 4 weeks of therapy and after completion of therapy with nicotinamide (at the end of 8 weeks) was done using paired *t*-tests. A *P*-value of <0.05 was considered significant.

Results

A total of 30 patients (23 patients on twice weekly and 7 on thrice weekly dialysis) were included in the study. The study population consisted of 20 (66.7%) males and 10 (33.3%) females, aged above 20 years, with a mean age of 54±14.9 years. Majority of the patients were in the age range of 41– 60 years (13 patients).The most common co-morbidity was hypertension in 20 patients (66.7%), followed by diabetes in 8 (26.7%). Sixteen (53.3%) patients were taking calcium carbonate 500 mg thrice daily and 14 (46.7%) patients were taking calcium acetate 667 mg thrice daily as phosphate binders before the washout period of 2 weeks [Table 1].

Twenty-five patients (10 women and 15 men) with serum phosphorus >5 mg/dL were given niacinamide 250 mg twice daily and 5 patients (1 woman and 4 men) with serum phosphorus >8 mg/dL were given nicotinamide 250 mg thrice daily immediately after meals for 8weeks. There was a significant reduction ($P < 0.001$) in the mean serum phosphorus levels after 4 weeks of drug treatment

and after 8 weeks of drug treatment when compared to the serum phosphate levels at the baseline. Serum phosphate levels decreased from 6.85 ± 1.35 mg/dL at the baseline to 5.74 ± 1.18 mg/dL at the 4th week and then to 4.54 ± .86 mg/ dL at the 8th week of nicotinamide therapy [Table 2].

The mean serum calcium × phosphorus product decreased from 57.8 ± 12.21 at the baseline to 48.3 ± 10.71 on 4th week and 38.20 ± 8.21 on 8th week of nicotinamide treatment [Table 3].

Table 4 shows the laboratory results of the patients at the baseline and eight weeks after therapy. Serum calcium almost remained unchanged during the 8 weeks of nicotinamide treatment showing the levels of 8.42 ± 0.46 mmol/L before and 8.423 ± 0.52 mmol/L after treatment. There was no change in serum calcium level during the study period. BUN, creatinine, and uric acid levels showed no significant change during the study period. But there was a significant reduction in alkaline phosphatase levels during nicotinamide treatment period, from 130.23 ± 50.13 IU/L at the baseline to 116.40 ± 48.27 IU/L after 8weeks of treatment.

There were no changes in platelet count, liver function, blood sugar levels, BUN, uric acid, creatinine, serum protein and albumin levels. Watery stools were reported by seven patients when the drug was introduced, which later resolved during the course of the therapy.

Table 1: Baseline characteristics of study population

Characteristics	No. of patients (*N* = 30)	Percentage
Age range (years)		
20-40		
Males	2	6.7
Females	4	13.3
41-60		
Males	7	23.3
Females	6	20
>60		
Males	11	36.7
Females	–	–
Co-morbidities		
Hypertension (HTN)	20	66.7
Diabetes mellitus (DM)	8	26.7
DM/HTN/hypothyroidism	1	3.3
DM/HTN/tuberculosis	1	3.3
Phosphate binders used		
Calcium acetate (667mg)	14	46.7
Calcium carbonate (500mg)	16	53.3

Table 2: Mean serum phosphorus after 4 and 8 weeks after niacinamide treatment

Duration of therapy (*N* = 30)	Serum phosphorus levels (mg/dL)	*P* value
Baseline	6.8 ± 1.3513	
After 4 weeks	5.7 ± 1.1886	<0.001
End of 8 weeks	4.5 ± 0.8668	<0.001

Table 3: Serum Ca × P after 4 and 8 weeks of after niacinamide treatment

Duration of therapy (*N* = 30)	Serum Ca × P product	*P* value
Baseline	57.8 ± 12.2176	
After 4 weeks	48.3 ± 10.7176	<0.001
End of 8 weeks	38.2 ± 8.2137	<0.001

Table 4: Biochemical parameters before and after the niacinamide treatment

Biochemical Parameters (*N* = 30)	At baseline	After treatment	*P* value
Serum calcium (mg/dL)	8.4 ± 0.4659	8.4 ± 0.5217	1.000
Alkaline phosphatase (IU/L)	130 ± 50.132	116 ± 48.276	<0.001
BUN (mg/dL)	49 ± 19.170	47 ± 18.989	0.740
Serum creatinine (mg/dL)	8.8 ± 3.869	7.5 ± 3.0423	0.287
Uric acid (mg/dL)	5.7 ± 1.5787	5.7 ± 1.3922	1.000

Discussion

Niacin, first isolated from rice bran in 1911 and more commonly known as vitamin B3, is a water soluble vitamin with a recommended daily allowance of 0.3 mg/kg/day. It was later recognized to have two distinct but chemically related components, nicotinamide and nicotinic acid. Niacin deficiency causes pellagra in man.

Nicotinamide was first isolated from the horse erythrocytes in 1935, and is a component of NAD, a coenzyme involved in many cellular oxidative reduction reactions. NAD is proposed to be an intracellular inhibitor of sodium-dependent phosphate transport. Nicotinamide has been shown in rats to increase the renal cortical NAD concentration, to inhibit phosphate uptake by brush border membrane vesicles of the renal proximal tubules in the rat kidney, and to increase phosphate excretion in thyroparathyroidectomized rats.[21,22]

Nicotinamide is now known to inhibit sodium/ phosphorous transport in both renal and intestinal brush borders, stimulating interest in its use for phosphorus reduction among patients with CKD. In this connection, several studies have been performed and have shown that nicotinamide does decrease phosphorus levels in dialysis patients.[36-39]

The present study has yielded positive results with oral nicotinamide in reducing serum phosphorus levels substantially. A statistically significant decrease of mean serum phosphorus was found at the 4th and at the end of 8th week of nicotinamide therapy.

We maintained the doses at the same level for a period of 8 weeks to see whether the serum phosphorus levels decreased irrespective of the increase in doses. A significant decrease in mean phosphorus levels was observed in 4 weeks and further decrease was noted at the end of 8 weeks. This is quite distinct from other studies where the doses were increased every 2 weeks during the study.

In this study, no other phosphate binders were co-administered along with nicotinamide to reduce the phosphate levels, which correlated with the findings of Takahashi[38] and Sampathkumar,[39] who demonstrated that nicotinamide lowers serum phosphorus levels in maintenance HD patients even when traditional binding agents are withheld. But this is not in concordance with the study conducted by Cheng,[37] who concluded that nicotinamide reduces serum phosphorus when co-administered with other phosphate binders.

In the present study, a statistically significant decrease in mean serum Ca × P product was observed in 4 weeks and further decrease was observed at the end of 8 weeks. This is in accordance with other studies that had observed a concurrent fall in the Ca × P product during the nicotinamide treatment. But there were no changes in serum calcium and uric acid levels with nicotinamide treatment at the end of 8 weeks which is similar to that reported in the literature.[36-39]

There was a slight decrease in mean creatinine and BUN levels, which was not statistically significant. Eto,[21] in an experimental study on rats with adenine-induced renal failure, reported that nicotinamide had protective effect against the deterioration of renal function by preventing the increase in BUN, serum creatinine levels and also increased the creatinine clearance in rats.

Regarding the adverse drug reactions of nicotinamide, watery stools were reported in seven patients and it resolved on continuation of therapy not requiring any dosage adjustment or therapy with other drugs. Thrombocytopenia that is commonly associated with niacinamide and nicotinic acid therapy was not reported by any of the patients. Other than alkaline phosphatase levels all the liver function tests were normal. Blood sugar levels were also not affected by nicotinamide therapy. Delanaye,[40] showed the occurrence of diarrhea in five of six patients enrolled in an open-label trial on the safety and efficacy of nicotinamide. The symptoms began at a mean nicotinamide dosage of 1050 ± 447 mg and resolved after drug cessation. In the study done by Takahashi,[38] the study cohort developed diarrhea when nicotinamide was administered alone and one patient showed statistically significant decrease in platelet count during nicotinamide treatment. However after washout the platelet count returned to pretreatment level.

Nicotinamide was also found to be a cost-effective therapy for hyperphosphatemia in HD as the cost of a nicotinamide 250 mg tablet (generic) was less than ₹1.00, whereas the costs of the other phosphate binders are as follows: ₹3.00 per tablet for nicotinic acid 375 mg (brand used: Nialip); calcium acetate 667 mg (brand used: Phostat) and calcium carbonate 500 mg (brand used: Shelcal); ₹16.50 per tablet for sevelamer hydrochloride 400 mg (brand used: Foseal) and ₹16.00 per tablet for Lanthanum carbonate 500 mg (brand used: Lanthonate).

The study had few limitations like short duration, small number of cases and non-estimation of lipid profile, parathyroid hormone levels and serum NAD concentrations due to financial constraints.

Conclusion

The present study shows that nicotinamide is safe and effective in controlling serum phosphorus, Ca × P product and alkaline phosphatase levels.

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