Peritoneal Dialysis International, Vol. 29, pp. 562–567
Printed in Canada.

0896-8608/09 $3.00 + .00

THE EFFECT OF ORAL NIACINAMIDE ON PLASMA PHOSPHORUS LEVELS IN PERITONEAL DIALYSIS PATIENTS

Daniel O. Young, Steven C. Cheng, James A. Delmez, and Daniel W. Coyne

Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri, USA

♦♦ ***Background:*** **Hyperphosphatemia remains a significant problem for patients requiring dialysis and is associated with increased mortality. Current treatment options include dietary restriction, dialysis, and phosphate binders. Treatment using the latter is frequently limited by cost, tolerability, and calcium loading. One open-label trial found niacinamide to be effective at decreasing serum phosphorus values in hemodialysis patients. Niacinamide may effectively reduce phosphorus levels in peritoneal dialysis (PD) patients already receiving standard phosphorus-lowering therapies.**

♦♦ ***Methods:*** **An 8 week, randomized, double blind, placebo-controlled trial to evaluate the effectiveness of niacinamide to reduce plasma phosphorus levels in PD patients. Patients had to demonstrate a baseline phosphorus value > 4.9 mg/dL. Patients were randomized to niacinamide or placebo and prescribed 250 mg twice daily, with titration to 750 mg twice daily, as long as safety parameters were not violated. Phosphate binders, active vitamin D, and cinacalcet were kept constant during the study. The primary end point was change in plasma phosphorus. Secondary end points included changes in lipid parameters.**

♦♦ ***Results:*** **15 patients started on the study drug (8 niacinamide, 7 placebo) and 7 in each arm had at least one on-study phosphorus measurement. The niacinamide treatment group experienced an average 0.7 ± 0.9 mg/dL decrease in plasma phosphorus and the placebo-treated group experienced an average 0.4 ± 0.8 mg/dL increase. The treatment effect difference (1.1 mg/dL) was significant ($p = 0.037$). No significant changes in high- or low-density lipoproteins or triglycerides were demonstrated. Two of the 8 patients randomized to the niacinamide treatment arm had to withdraw from the study due to drug-related adverse effects. Adverse effects may limit the use of niacinamide in PD patients.**

♦♦ ***Conclusion:*** **Niacinamide, when added to standard phosphorus-lowering therapies, resulted in a modest yet statistically significant reduction in plasma phosphorus levels at 8 weeks. [ClinicalTrials.gov number NCT00508885 (ClinicalTrials.gov)]**

Perit Dial Int **2009; 29:562–567** **www.PDIConnect.com**

KEY WORDS: Hyperphosphatemia; phosphorus; niacin; niacinamide; nicotinamide; secondary hyperparathyroidism; renal osteodystrophy; chronic kidney disease.

Hyperphosphatemia remains a common problem in patients receiving maintenance dialysis and contributes to the development of secondary hyperparathyroidism. Current therapies for the treatment of hyperphosphatemia are frequently insufficient to achieve the currently recommended K/DOQI goal of maintaining a serum phosphorus level between 3.5 and 5.5 mg/dL (1) in patients on hemodialysis (HD) or peritoneal dialysis (PD). Approximately 60% of HD patients have phosphorus levels above the upper recommended limit (2). Additionally, hyperphosphatemia has been associated with increased mortality in multivariate models (3).

Niacin, or nicotinic acid, is also known as vitamin B3. Niacin is a water-soluble vitamin critical for cell energy metabolism. Niacinamide (or nicotinamide) is the corresponding amide form of niacin. Niacinamide is thought to possess less potential for side effects, namely flushing, than niacin. Animal studies have suggested that niacinamide may decrease brush border uptake of phosphate by blocking the sodium phosphate co-transporter (4) in the small intestine. Recent clinical trials suggest that niacin and niacinamide have potential for decreasing serum phosphorus levels in HD patients (5,6); however, these studies were neither randomized nor blinded, subjecting the results to bias. More recently, another non-blinded prospective study found that Niaspan (Kos Life Sciences, Mississauga, ON, Canada), at a mean dose of 1470 mg daily, decreased

Correspondence to: D. Young, Renal Division, Washington University School of Medicine, 660 S. Euclid Ave., Box 8129, St. Louis, Missouri 63110 USA.
danieloyoung@hotmail.com
Received 26 March 2008; accepted 8 September 2008.

serum phosphate levels by 1.3 mg/dL (7). Niacinamide has potential advantages over current phosphate binders in that it does not need to be administered at the time of a meal, could potentially reduce treatment costs, and may improve lipid parameters.

The present study was designed with the primary aim of evaluating whether niacinamide is effective in the treatment of hyperphosphatemia in patients on PD. The primary end point was the absolute change in plasma phosphorus between treatment groups. Secondary end points included the percent change in plasma phosphorus, change in calcium–phosphorus product (Ca×P), and changes in high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides.

METHODS

STUDY DESIGN AND PROTOCOL

This study was approved by the Human Subjects Committee of the Washington University School of Medicine (Protocol # 06-0462). Written informed consent was obtained from all patients enrolled in the study. This study is registered at ClinicalTrials.gov (ClinicalTrials.gov number NCT00508885).

This study was an 8 week, prospective, randomized, double-blind placebo-controlled trial to evaluate the effectiveness of niacinamide versus placebo in reducing plasma phosphorus levels in PD patients. Study screening began in the fall of 2006. At that time, the PD clinics at Washington University School of Medicine had a census of 53 patients. All patients were screened for inclusion by their most recent monthly plasma phosphorus value.

Inclusion criteria were age >18 years, capable of giving informed consent, duration of PD >3 months, dose of phosphate binder(s) stable over the previous 2 weeks, and plasma phosphorus >4.9 mg/dL based on the most recent laboratory data within 1 month of enrollment. Exclusion criteria were pregnancy, known liver disease, active peptic ulcer disease, treatment with carbamazepine, current medication including or previous intolerance to either niacin or niacinamide, planned surgical procedure within the next 4 months, and patients in nursing homes or extended care facilities where administration of the study drug may not be appropriately given. Patients with phosphorus values >3.9 mg/dL meeting all other inclusion criteria were eligible for consenting and a reduction in the current phosphate binder dose, repeat screening within 2 – 4 weeks, and continued participation if the repeat phosphorus value exceeded 4.9 mg/dL.

Patients were randomized at the time of consent in 4 × 4 permuted blocks up to 16 patients. After 16 patients had been consented, randomization then occurred in 2 × 2 permuted block enrollment. The research pharmacist who prepared the study medication and placebo capsules also performed patient randomization. Niacinamide (250 mg per capsule) and placebo were packaged as identically appearing capsules.

Study medication or placebo was started at 250 mg twice daily, increased to 500 mg twice daily after 2 weeks and to 750 mg twice daily after 4 weeks, and continued until study completion. Changes in phosphate binder dose were not allowed except if phosphorus values exceeded 6.5 mg/dL or fell below 3 mg/dL. Active vitamin D and cinacalcet doses were required to remain stable.

LABORATORY METHODS

To minimize technique and assay variability, all non-screening study laboratory value testing represented in this paper was performed at the Barnes–Jewish Hospital laboratory. Available test results were reviewed within 24 hours of collection. Calcium, albumin, and phosphorus values were collected every 2 weeks; complete blood counts were collected every 4 weeks; cholesterol panels, intact parathyroid hormone (iPTH), and uric acid were collected at study drug start and end. If a patient was withdrawn from the study prior to week 8, all the above laboratory studies were collected from patients as soon as possible. Last observation carried-forward phosphorus values represent only those measurements recorded while patients were actively taking the study medication. The average of each patient's screening phosphorus and week 0 phosphorus was used as a baseline for comparison to the final study phosphorus value.

STATISTICS

Power analysis calculations demonstrated that 16 patients (8 per treatment arm) would be needed for this prospective study to achieve 80% power at the 5% significance level utilizing a two-sided analysis and assuming an expected phosphorus difference of 1.5 mg/dL (standard deviation assumed to be 1.0 mg/dL). Up to 20 recruited patients were anticipated to account for potential dropouts and study withdrawals.

Descriptive statistics that used means and standard deviations are presented as continuous variables. Independent and paired samples t-test and Fisher's exact test were applied to normally distributed continuous data and categorical data respectively. The Mann–Whitney U test and the Wilcoxon signed rank test were applied to

independent and paired continuous data that were not normally distributed.

Analyses were done by intention-to-treat (ITT) with the last observation carried forward. Patients were included if they had completed at least 2 weeks of study medication and had at least one post-baseline plasma phosphorus value. A two-tailed $p < 0.05$ was considered statistically significant for all tests. Statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Seventeen patients were consented and randomized to participate in the study (Figure 1). Two in the placebo arm were withdrawn prior to study drug because of re-screening phosphorus levels <5 mg/dL after phosphate binder dose reduction. One patient in the niacinamide arm was withdrawn after 2 days of study drug due to severe diarrhea. Seven patients in each treatment arm were ultimately included in the ITT analysis (Figure 1). Patients' demographics and baseline characteristics (Table 1) were not significantly different between the groups.

EFFECT OF NIACINAMIDE ON PHOSPHORUS CONTROL

No changes in phosphate binder were needed by study participants in either treatment arm once the study medication had been initiated. Overall, 5 of 7 patients in the placebo group experienced an increase in their plasma phosphorus values compared to 1 of 7 patients treated with niacinamide. The average increase from baseline in plasma phosphorus was 0.4 ± 0.8 mg/dL in the placebo group whereas the niacinamide-treated group experienced a 0.7 ± 0.9 mg/dL decrease (absolute difference of 1.1 mg/dL between the two treatment groups, $p = 0.037$) (Table 2). (To convert phosphorus from mg/dL to mmol/L, multiply the value by 0.3229.) Overall, treatment with niacinamide lowered phosphorus levels by 10.9%, while the placebo treatment group experienced an average phosphorus level increase of 8.9% (difference 19.6%, $p = 0.029$) (Figure 2).

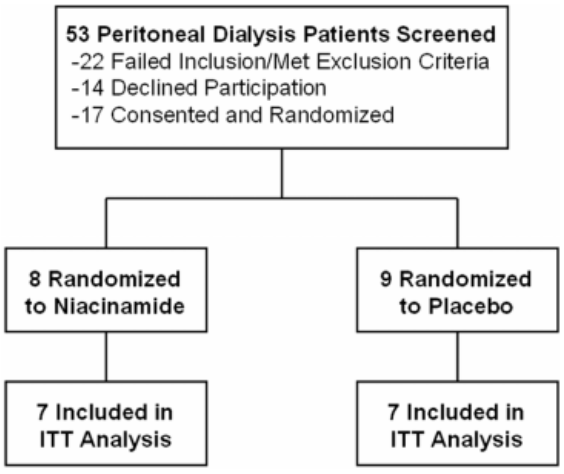

Figure 1 — A schematic of patient disposition. ITT = intention-to-treat.

EFFECT OF NIACINAMIDE ON SECONDARY END POINTS

No statistically significant changes in lipid parameters were observed in this study. Notably, no increase in HDL cholesterol was demonstrated in the niacinamide treatment group (Table 3). Additionally, no statistically significant changes were demonstrated for changes in Ca×P or iPTH values.

SIDE EFFECTS

One patient randomized to niacinamide discontinued the study medication after 2 days due to severe diarrhea. She was not included in the analyses. Another patient randomized to niacinamide was removed from the study at 4 weeks by his treating physician due to a pruritic rash, which improved after discontinuation of the study medication. One patient in the placebo group withdrew from the study shortly after his week-4 visit due to flushing attributed by the patient to the study medication. There was a statistically significant increase in mean uric acid levels among the niacinamide-treated participants (from 7.2 to 7.6 mg/dL, $p = 0.035$; Table 3). The increase in mean white blood cell count (from 9.2 to 10.6 × $10^3/mm^3$) and decrease in hemoglobin (from 12.2 to 11.4 g/dL) with niacinamide approached statistical significance ($p = 0.077$ and $p = 0.064$ respectively). There were no episodes of thrombocytopenia noted with niacinamide treatment.

DISCUSSION

In 2004, Takahashi and colleagues reported their experience with niacinamide (5). In their study, 65 HD patients given a mean dose of 1080 mg niacinamide per day experienced a 1.5 mg/dL decrease in serum phosphorus after a 2-week washout of calcium carbonate followed by 12 weeks of treatment with niacinamide. The patients experienced significant decrease in mean iPTH levels and average HDL levels increased from 47.4 to 67.2 mg/dL.

Another prospective open-label trial of 34 HD patients found that nicotinic acid, in an initial dose amount of

TABLE 1
Demographic and Baseline Clinical Characteristics in All and Each Group of Patients

	All patients (*n*=14)	Niacinamide group (*n*=7)	Placebo group (*n*=7)	*p* Value
Age (years)	53.4±10.9	51.1±10.3	55.7±11.8	0.46
Gender (M/F)	12/2	5/2	7/0	0.46
PD vintage (months)	18±11	16±12	20±16	0.43
Modality (CCPD/CAPD)	12/2	6/1	6/1	1.00
Total Kt/V	2.17±0.54	2.40±0.67	1.95±0.24	0.12
PD Kt/V	1.68±0.47	1.58±0.60	1.78±0.31	0.46
PCR (g/kg/day)	0.81±0.28	0.90±0.38	0.71±0.11	0.24
Phosphate binder use (*n*)	13	6	7	1.00
Sevelamer use	7	3	4	1.00
Calcium-based binder	4	3	1	0.56
Statin use (*n*)	10	6	4	0.56

PD = peritoneal dialysis; CCPD = continuous cycling PD; CAPD = continuous ambulatory PD; PCR = protein catabolic rate.
Numerical values presented as mean±standard deviation.

TABLE 2
Average Plasma Phosphorus Values by Study Week and Treatment Assignment

	Plasma phosphorus (mg/dL)				
	Week 0	Week 2	Week 4	Week 6	Week 8[a] (LOCF)
Niacinamide treatment group	5.9±0.6	5.1±1.0	5.1±0.9	5.7±0.9	5.2±0.9
Average change from baseline		−0.8±0.8	−0.8±0.9	−0.4±0.7	−0.7±0.9
Placebo treatment group	5.5±0.5	5.4±0.7	5.6±0.8	6.0±1.3	5.9±0.4
Average change from baseline		−0.1±1.2	0.1±0.8	0.4±1.2	+0.4±0.8
Absolute difference in change between groups		0.7	0.9	0.8	1.1
p Value					0.037

[a] Week 8 represents last observation carried forward (LOCF) values.
Numerical values presented as mean±standard deviation. To convert phosphorus from mg/dL to mmol/L, multiply value by 0.3229.

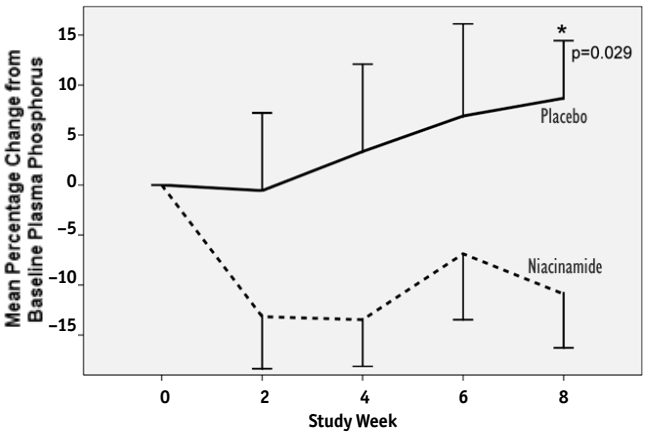

Figure 2 — Mean percentage change from baseline plasma phosphorus in placebo-treated subjects (solid line) and niacinamide-treated subjects (broken line). Week 8 represents the intention-to-treat last observation carried forward analysis of percentage change. Error bars represent ±1 SE.

375 mg daily, resulted in a 2.1 mg/dL average decrease in serum phosphorus levels (6). All patients underwent a 1-week washout of all phosphate binders and the study medication was administered for 8 weeks. A significant change in Ca×P was also noted. Lipid information and iPTH data were not available.

This study is the first to examine the impact of niacinamide on plasma phosphorus levels in PD patients. A modest yet statistically significant difference in mean plasma phosphorus of 1.1 mg/dL was demonstrated. Unlike the prospective studies noted above, all patients except for 1 in the niacinamide treatment group continued to take their regularly prescribed phosphate binders, potentially limiting the treatment effect of niacinamide. The percent change between the two treatment groups was 19.6%. This is comparable to the 22% reduction in serum phosphorus Takahashi demonstrated after 12 weeks of treatment with niacinamide (5). The absolute treatment effect is comparable to that seen by

TABLE 3
Baseline and Study Completion Laboratory Values by Treatment Group

	Niacinamide group (*n*=7)		Placebo group (*n*=7)	
	Week 0	Week 8[a] (LOCF)	Week 0	Week 8[a] (LOCF)
Plasma phosphorus (mg/dL)	5.9±0.6	5.2±0.9	5.5±0.5	5.9±0.4
Serum albumin (g/dL)	3.9±0.2	3.8±0.4	4.0±0.3	4.0±0.3
Corrected calcium (mg/dL)	9.4±0.4	9.7±0.6	9.9±0.7	9.9±0.6
Calcium × phosphorus product (mg^2/dL^2)	55.0±6.6	55.2±18.5	54.5±7.2	58.0±3.5
Uric acid (mg/dL)	7.2±1.0	7.6±0.9	6.1±1.3	6.3±0.9
Intact parathyroid hormone (pg/mL)	407 (143–539)	305 (176–533)	178 (23–631)	146 (57–728)
WBC count ($\times 10^3/mm^3$)	9.2±1.5	10.6±2.2	9.4±2.9	9.1±1.7
Hemoglobin (g/dL)	12.2±0.8	11.4±0.8	11.6±0.5	11.3±0.9
Platelet count ($\times 10^3/mm^3$)	276±59	272±58	238±72	245±71
Total cholesterol (mg/dL)	152±34	153±56	142±25	148±32
HDL cholesterol (mg/dL)	48±13	48±16	39±10	38±7
LDL cholesterol (mg/dL)	63±30	69±49	62±22	68±32
Triglycerides (mg/dL)	207±93	175±58	227±79	232±125

WBC = white blood cell; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LOCF = last observation carried forward.
[a] Week 8 represents LOCF values.
Numerical values presented as mean±standard deviation or mean (range). To convert phosphorus from mg/dL to mmol/L, multiply value by 0.3229.

other investigators (5,7) including our own experience with HD patients (8).

In contrast to Takahashi's findings, lipid parameters were essentially unaffected in the present study. There may be several reasons for the finding in addition to underpowering for secondary end points. In one of the initial clinical studies to evaluate the effect of niacin on cholesterol profiles, nicotinic acid resulted in a significant reduction in total cholesterol, whereas niacinamide had no effect (9). Alternatively, 3 patients in the niacinamide-treated group were taking sevelamer, which lowers total and LDL cholesterol (10) by functioning as a bile resin. Also, 6 patients in the niacinamide-treated group were being administered statins. It is possible the lipid-altering effect of niacinamide may be diminished or abolished in patients that are concurrently administered a statin and/or sevelamer. Also, nicotinamide has a molecular weight of 122.125 Da, making the potential for continuous removal by PD likely. This could also partially explain the less dramatic phosphorus-lowering treatment effect. Furthermore, comparing lipid changes in HD patients to PD patients may be difficult due to the glucose load and continuous protein losses with PD. Additionally, although the mean HDL level in our study did not change significantly, fluctuations in individual levels were noted.

Known side effects of niacin include thrombocytopenia and an increase in uric acid (11). Niceritrol, an ester pro-drug of niacin, was shown in one case report to result in a significant drop in hemoglobin and platelet count in a HD patient (12). The mechanisms for thrombocytopenia and anemia have not been elucidated. In this study, a small, yet statistically significant increase in the uric acid ($p = 0.035$) level was observed. The patients randomized to the niacinamide treatment arm had higher levels of residual renal function than did patients in the placebo-treated group, thus making the likelihood of finding an increase in the uric acid level more likely. Additional study is needed to confirm if the increase in uric acid observed in PD patients is real.

A trend toward reduced mean hemoglobin in the niacinamide-treated group was demonstrated ($p = 0.064$). Although our study did not prohibit changes in iron and epoetin administration, a review of the patients' charts revealed no change in epoetin dosage or evidence of iron deficiency as manifest by a transferrin saturation <20% during the study period. There were no episodes of decreasing platelet counts.

A high rate of adverse effects due to niacinamide was seen in this short study and the change in phosphorus was only slightly less robust than reported by other authors (5–7). However, our patients continued to take their previously prescribed phosphate binders and a significant albeit modest effect remained apparent. This randomized single-center study confirms the results of previous nonrandomized prospective studies and adds to the present literature by restricting our study population solely to PD patients.

In summary, short term, twice daily, oral niacinamide administration resulted in a modest yet statistically significant decrease in mean plasma phosphorus levels in PD patients. Additional, large scale, multicenter, randomized, double-blinded placebo-controlled trials of longer duration are warranted to further validate the phosphorus-lowering efficacy of niacinamide and critically examine the safety profile of this promising therapy.

DISCLOSURE

The National Kidney Foundation of Eastern Missouri and Metro East, Inc., provided D.O. Young with a research grant to cover all costs associated with this clinical trial. This funding organization had no role in the collection of data, its analysis and interpretation, or any right to approve or disapprove publication of the finished manuscript.

ACKNOWLEDGMENTS

D.O. Young received a research grant from the National Kidney Foundation of Eastern Missouri and Metro East, Inc., and a Nephrology Fellowship Stipend support from Amgen for the 2006–2007 academic year.

Portions of this work were presented in abstract form at the North American Chapter of the International Society for Peritoneal Dialysis meeting in Hollywood, Florida, June 1 – 3, 2007.

REFERENCES

1. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42(4 Suppl 3):S1–201.
2. Block GA, Port FK. Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. *Am J Kidney Dis* 2000; 35:1226–37.
3. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; 31:607–17.
4. Katai K, Tanaka H, Tatsumi S, Fukunaga Y, Genjida K, Morita K, *et al*. Nicotinamide inhibits sodium-dependent phosphate cotransport activity in rat small intestine. *Nephrol Dial Transplant* 1999; 14:1195–201.
5. Takahashi Y, Tanaka A, Nakamura T, Fukuwatari T, Shibata K, Shimada N, *et al*. Nicotinamide suppresses hyperphosphatemia in hemodialysis patients. *Kidney Int* 2004; 65: 1099–104.
6. Sampathkumar K, Selvam M, Sooraj YS, Gowthaman S, Ajeshkumar RN. Extended release nicotinic acid—a novel oral agent for phosphate control. *Int Urol Nephrol* 2006; 38:171–4.
7. Muller D, Mehling H, Otto B, Bergmann-Lips R, Luft F, Jordan J, *et al*. Niacin lowers serum phosphate and increases HDL cholesterol in dialysis patients. *Clin J Am Soc Nephrol* 2007; 2:1249–54.
8. Cheng SC, Young DO, Huang Y, Delmez JA, Coyne DW. A randomized, double-blind, placebo-controlled trial of niacinamide for reduction of phosphorus in hemodialysis patients. *Clin J Am Soc Nephrol* 2008; 3:1131–8.
9. Altschul R, Hoffer A, Stephen JD. Influence of nicotinic acid on serum cholesterol in man. *Arch Biochem* 1955; 54: 558–9.
10. Manns B, Stevens L, Miskulin D, Owen WF Jr, Winkelmayer WC, Tonelli M. A systematic review of sevelamer in ESRD and an analysis of its potential economic impact in Canada and the United States. *Kidney Int* 2004; 66:1239–47.
11. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol* 2007; 99(6A):22C–31C.
12. Wakasugi H, Futami T, Muso E, Ono T, Sasayama S, Inui K. Thrombocytopenia and anemia induced by niceritrol used for amelioration of hyperphosphatemia in a hemodialysis patient. *Nephron* 2000; 86:97–8.