Association of Niacin on Phosphate Control in Advanced-Stage Chronic Kidney Disease Patients within a VA Population

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Abstract

Current options for lowering phosphate levels have many limitations. A novel approach for treating hyperphosphatemia is the use of niacin therapy, which has been shown to decrease serum phosphorus by inhibiting type IIb sodium-phosphate cotransporter in the gastrointestinal tract. The primary objective of this study was to compare phosphorus control in patients with advanced stages of CKD who received or did not receive niacin.

Male patients aged 18 years or older at the Edward Hines, Jr. VA Hospital with CKD stage 4 or 5 or ESRD between January 1, 2011 to December 31, 2014 who were actively followed within the Hines VA renal clinic and had at least three phosphorus levels within six months were included in the study. The primary endpoint was median phosphorus control between patients receiving or not receiving niacin with pill burden from phosphate binders being the secondary endpoint.

Niacin therapy was associated with a clinically and statistically significant difference in phosphate level. There was a trend suggesting niacin may reduce the pill burden of phosphate binders, however this was not statistically significant. In light of these results, further examination with longer data collection windows or with different VA facilities is being considered.

Introduction

Hyperphosphatemia is highly prevalent in CKD and has been reported to occur in up to 25% of patients with CKD stage 4 and 50% of patients with CKD stage 5 (1,2). As kidney function declines, phosphorus excretion and vitamin D activation are reduced. This decreases calcium absorption from the gastrointestinal (GI) tract and disturbs the balance of calcium and phosphorus (3). In response, the parathyroid glands release parathyroid hormone (PTH). The actions of PTH include the following: increasing calcium resorption from the bone, increasing calcium reabsorption and decreasing phosphorus reabsorption from the proximal tubules in the kidneys, and stimulating the activation of vitamin D to calcitriol. Calcitriol promotes calcium absorption in the GI tract, increases calcium mobilization from bone, and decreases PTH levels through negative feedback. The net result is elevated serum calcium and reduced phosphorus levels. However, as kidney function continues to decline to CKD stage 3 and beyond, the regulatory processes, such as phosphorus excretion and vitamin D activation, do as well. Increased serum phosphorus binds to calcium, which, at high enough levels, can cause vascular calcification. These changes, if left untreated, have been shown to lead to secondary hyperparathyroidism, tissue calcification, and higher cardiovascular (CV) mortality (4,5). It has been reported that the risk of CV mortality can increase up to 18% with every 1 mg/dL increase in serum phosphorus above the normal range of 2.5-4.5 mg/dL in healthy adults (6).

Current options for lowering phosphate levels have many limitations. First, not every patient with CKD requires dialysis, and dialysis is insufficient on its own to maintain serum phosphorus levels (4). Second, rigid dietary restriction of phosphorus is often not feasible given that the phosphate content in food can be difficult to determine, and many phosphate additives are highly bioavailable. Additionally, many foods that contain a high content of phosphorus are also rich in protein. Although protein restriction is recommended for individuals with non-dialysis CKD in order to delay progression of kidney disease, protein needs for those with dialysis-dependent CKD stage 5 are increased. As a result, a potential risk of dietary phosphate restriction is malnutrition (4,7). Third, the main pharmacological treatment option is phosphate binders, which bind to ingested phosphate in the GI tract. This results in decreased phosphate absorption through the formation of insoluble complexes that are excreted in the feces. Due to this mechanism of action, typical dosing involves multiple tablets taken with each meal and snack throughout the day. Phosphate binders are often associated with GI side effects and a large pill burden (3). In one study, the median daily pill burden was 19 in chronic dialysis patients (8). The daily pill burden exceeded 10 in 91% of subjects, was more than 20 in 47% of subjects, and surpassed 30 in 17% of subjects. This study concluded that phosphate binders are the largest...
Niacin and Niacinamide Structures

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contributors to pill burden, accounting for approximately 50% of total medications. In addition, it found that this high pill burden was associated with significantly lower adherence and higher phosphorus levels. Adherence to phosphate binders can also be adversely affected by the requirement for dosing with meals and the cost of non-calcium containing binders. Although calcium-containing binders currently provide a more cost-effective alternative and are generally used as first-line agents, they impose the risk for high calcium load, which could contribute to vascular calcification and premature morbidity or mortality (2,7).

A novel approach for treating hyperphosphatemia in CKD is the use of niacin therapy. Niacin, a water-soluble vitamin, is bioconverted to nicotinamide adenine dinucleotide (NAD+), and the hydride equivalent (NADH) which are coenzymes necessary for tissue metabolism, lipid metabolism, and glycogenolysis (9). Approximately 50% of the net phosphate absorption occurs in the duodenum and jejunum through active transport involving type IIB sodium-phosphate cotransporters. Animal studies have shown that nicotinamide inhibits the expression of these transporters, which decreases phosphate absorption and prevents the progressive increase in phosphate levels associated with renal failure (4,6,10). According to the package insert, Niaspan® (extended release niacin) has been associated with small but statistically significant reductions in phosphorus levels (mean of -13% with 2000 mg daily) (11). Niacin is typically administered once or twice daily without regard to meals because it does not work by merely trapping food-bound phosphorus in the gut. Consequently, it offers a more convenient and flexible dosing regimen, which may increase patient adherence (4,6). Another potential benefit of niacin therapy is the availability of generic formulations, which provides a cost savings benefit compared to the non-calcium based binders and newer iron-based phosphate binders. Previous studies have demonstrated the effectiveness of immediate-release niacin in lowering serum levels of phosphorus. For instance, one study by Ahmadi and colleagues compared the efficacy of niacin with sevelamer in patients receiving hemodialysis (5). Forty patients with serum phosphate levels greater than 6 mg/dL underwent a two-week wash-out period and then were randomly assigned to either sevelamer (1600 mg in the morning and 1600 mg in the evening) or niacin IR (300 mg in the morning and 200 mg in the evening). After four weeks of treatment, the mean serum level of phosphorus was significantly reduced in both groups. Sevelamer reduced phosphorus from 6.9+/−1.05 mg/dL to 4.7+/−1.1 mg/dL (p < 0.0001) while niacin reduced phosphorus from 7.3+/−1.19 mg/dL to 5.6+/−1.6 mg/dL (p < 0.01). The serum calcium level remained unchanged in both treatment arms. In addition, an eight-week, double-blind, placebo-controlled, randomized clinical trial by Shabbazian, et al. demonstrated a statistically significant reduction in phosphorus with nicotinamide (also known as niacinamide) treatment (12). Forty-eight participants were randomly assigned to either a placebo or nicotinamide, which was given as 500 mg per day for the first four weeks and then 1000 mg per day for the second four weeks. Phosphorus levels significantly decreased from 5.9+/−0.58 mg/dL to 4.77+/−1.43 mg/dL (p < 0.01) after four weeks and then to 4.66+/−1.06 mg/dL (p < 0.001) after eight weeks of nicotinamide treatment. The authors from this study concluded that the effects of nicotinamide can be seen with even low doses if the duration is adequate.

Extended release niacin has also been shown to be effective in reducing serum levels of phosphorus. For example, a prospective study by Muller and colleagues analyzed the effects of prolonged-release niacin in dialysis patients (13). After a two-week washout period, participants were given 375 mg of Niaspan® daily. The dosage was increased every two weeks to 500, 1000, 1500, and 2000 mg daily. After twelve weeks of treatment, phosphate levels were significantly reduced from 7.2+/−0.5 to 5.9+/−0.6 mg/dL (p=0.015). The onset of effect was relatively rapid and seen within 14 days of treatment, presumably due to niacin’s mechanism of action on intestinal cotransporters and possible renal accumulation. Niacin had no effect on calcium levels, but it did increase HDL cholesterol from 40+/−3.2 to 59+/−5.5 mg/dL (p=0.0005). Additionally, a post hoc analysis of a double-blind, randomized, placebo-controlled trial by Maccubbin et al showed that niacin use for 24 weeks resulted in an approximately 11% sustained reduction in serum phosphorus and a 12% reduction in calcium-phosphorus product, which supports the use of niacin in reducing the risk for vascular calcification (14). In patients with an eGFR less than 60 mL/min/1.73m², baseline serum phosphorus (3.41+/−0.49 mg/dL) changed by -0.38 mg/dL (95%CI -0.47 to -0.29) with extended release niacin. In contrast, baseline serum phosphorus (3.46+/−0.45 mg/dL) increased by 0.03 mg/dL (95%CI -0.09 to -0.15) with a placebo.

Objective

Based on review of the literature, there is evidence supporting the use of niacin in hyperphosphatemia treatment as either monotherapy or as an additive agent to reduce the load of phosphate binders. The primary purpose of this study was to analyze phosphorus control in patients treated with niacin for any indication in a VA setting with advanced stages of CKD.

Methods

This study was a retrospective chart review of patients at the Edward Hines, Jr. VA Hospital with CKD stage 4 or 5 or ESRD between January 1, 2011 to December 31, 2014. Eligible patients for screening were identified via a fileman search of patients using ICD codes and medication orders for niacin (controlled-released nicotinic acid).
Inclusion criteria for the study included male patients 18 years of age or older, with a diagnosis of CKD stage 4 or 5, who have been followed actively within the renal clinic at Hines and have at least three phosphorus levels within a six month time period. Exclusion criteria included patients who have been using niacin in the treatment group for less than six months in general, or who have experienced either initiation or discontinuation of dialysis treatment during the time frame of data collection. Patients newly consulted to see a renal dietitian were also excluded to avoid confounding of phosphorus control from dietary modifications, but patients that were actively following with a renal dietitian were included. Patients were further excluded if they had been admitted to the hospital or extended care center within the six month time frame.

The primary outcome was phosphorus control, which was reflected as each subject’s average serum phosphorus level over the course of six months. This was used to calculate the median phosphorus level within each treatment group, which was then compared using the paired t-test. The pill burden from phosphate binders was also compared as a secondary endpoint. Sub-group analyses looked at differences in patient outcomes in: those with diabetes, those with concurrent aspirin use, those who had received a consult from the renal dietitian concerning dietary phosphorus restriction before the time frame of data collection, and those who were adherent with niacin therapy. Adherence was measured using the medication possession ratio (MPR), which divides the days’ supply of medication dispensed during a specified follow-up period by the number of days from the first dispensing to the end of the follow up period (15). A subject was considered adherent if greater than 80% of the expected number of pills were taken. Additionally, in subjects whose niacin therapy was started within the data collection period, a change in serum phosphorus was analyzed by recording a phosphorus level prior to niacin’s initiation and the average phosphorus after six months of therapy. For the secondary outcome/subgroup analyses, paired t-tests were used for continuous variables that had normally distributed data. For continuous data that was not normally distributed, the Wilcoxon signed rank sum test was utilized. For the categorical data, the McNemar test was applied, unless there were less than five observations and then the Friedman test for rank data was used.

Data collection targeted the most recent six month time period that did not meet any of the exclusion criteria. It included demographics (age, race), CKD diagnosis, etiology of kidney impairment, duration of dialysis if applicable, average SCr and eGFR, serum phosphorus levels, corrected calcium levels, use of phosphate binders, refill information for niacin, use of vitamin D analogs or calcimimetics, dietitian consult, aspirin use (in the niacin treatment group), serum albumin, glycated hemoglobin (A1C), average PTH, use of other active medications that may decrease phosphorus (i.e. calcium/vitamin D supplements, aluminum hydroxide, magnesium hydroxide, etc.), and documented adverse drug reaction or allergy to niacin. The control group was matched based on the level of kidney impairment; eligible patients were enrolled alphabetically.

Data from previous research studies was used to estimate the detectable difference in phosphorus control between the two groups. A standard deviation between 0.58 and 0.79 with a correlation between 0.1 and 0.5 was used to calculate the number of subject pairs needed to observe a difference in serum phosphorus levels documented in prior studies. With approximately 50 patients in each group, 80% power, and an alpha of 0.05, it was anticipated that a difference of 0.38 mg/dL in the median phosphorus level would be detected. This estimate used the standard deviation from previous clinical studies and therefore offered a conservative estimate of the detectable difference.

Results

A total of 5,430 patients had a diagnosis of CKD (based on the ICD-9 codes) during the data collection period. Of these, 531 either had a history of niacin use or were currently being prescribed niacin. The control group was comprised of the remaining patients (Figure 1). After reviewing the patients in the niacin group, 25 were included in the study based on the inclusion and exclusion criteria. In order to control for the level of kidney impairment as a possible confounding variable affecting phosphorus control, the two treatment groups were matched based on this characteristic. Baseline characteristics, including age, gender, and etiology of kidney impairment, were similar between the two treatment groups (Table 1).

With regards to the primary outcome, the median phosphorus level was statistically lower in the niacin group when compared to the control (3.5 mg/dL vs. 4.2 mg/dL; p < 0.01). There were two patients in the niacin group and 6 patients in the control who had an average serum phosphorus greater than 4.6 mg/dL (p = 0.13). The average daily dose of phosphate binders was not statistically different but favored niacin therapy (3.5 tablets per day in the niacin group vs. 5.8 tablets per day in the control group; p = 0.39). One possible explanation for why a statistical difference was not found with the secondary outcome was due to the small

![Figure 1](https://www.renalnutrition.org)
level (3.5 mg/dL vs. 4.3 mg/dL; p < 0.01). There were no statistical differences found with regards to the average corrected calcium levels (9.40 mg/dL in the niacin group vs. 9.37 mg/dL in the control; p = 0.84) or the average A1c (7.5% in both groups; p = 0.88). Statistically, yet not clinically, significant differences were found in the average albumin (3.7 g/dL in the niacin group vs. 3.4 g/dL in the control) and the average PTH (152 pg/mL in the niacin group vs. 222 pg/mL in the control; p = 0.02).

Ninety-six percent of patients had taken aspirin therapy concurrently with niacin, and only one patient had a documented allergy/adverse drug reaction to niacin. Only 56% of patients were considered adherent to niacin based on the MPR. A statistical difference was still found in favor of niacin therapy when comparing the median phosphorus level between those patients who were considered adherent to niacin and the control (3.4 mg/dL vs. 4.2 mg/dL; p < 0.01). When analyzing patients who had started niacin therapy within the data collection period, the serum phosphorus decreased by 0.9 mg/dL. No correlation was found between the dose of niacin and the median phosphorus level (p = 0.95) (Figure 3).

Figure 2 – Subgroup Analyses

Figure 3 – Niacin Dose and Phosphorus Level

Discussion

Niacin was associated with a clinically and statistically significant difference in serum phosphorus levels. Similar findings were seen when assessing patients who were adherent with niacin based on the MPR. No correlation was found between the dose of niacin and the phosphorus level, which is similar to the findings from prior studies. Although a statistical difference was not found with the secondary endpoint, niacin may also reduce the load of phosphate binders. This is supported by the fact that a clinically significant decrease in phosphorus control was seen in the analysis of patients who had started niacin therapy within the 6 months of study enrollment. In addition, no difference was noted in A1c control, despite the risk of increased glucose levels with niacin use. However, caution is still warranted in patients with diabetes, gout, or peptic ulcer disease. From our review, nearly all of the patients who were receiving niacin,
controlled-release nicotinic acid, were on this as part of their lipid
management regimen by a non-renal provider. There were a small
number of patients who were prescribed niacin specifically for the
indication of managing hyperphosphatemia. These patients were
those who demonstrated poor tolerance or adherence to phosphate
binders, or were already receiving maximum recommended doses.

Conclusion

The strengths of this study include the following: controlling for
outliers in phosphorus control by comparing median levels,
assessing the use of phosphate binders as a secondary endpoint
(which was not seen in prior studies), and evaluating safety (i.e.
A1c, allergy to niacin, aspirin use). This study was limited by the
fact that it had a retrospective design and did not meet the pre-
specified enrollment number. In addition, only 56% of patients
were adherent with niacin based on the MPR, and a very limited
number of patients had uncontrolled phosphorus levels (based on
an average serum phosphorus greater than 4.6 mg/dL). This may
have impacted the generalizability of the results.

Niacin may offer an option to limit healthcare costs, minimize
side effects, and have an alternative mechanism of action for
phosphorus control than standard phosphate binders. Although
all niacin orders in this study were from prescriptions, there is the
option for extended-release niacin that can be purchased over-
the-counter. Further randomized clinical trials are warranted to
assess its full effect given the many variables for phosphorus
control, including the high pill burden and adherence issues with
many CKD patients. Additionally, longer collection data windows
with a larger patient population, along with an analysis of the
pharmacoeconomic impact of niacin’s use are well warranted.

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Check out this article in the RNF archives (www.renalnutrition.org):

Niacin: A Method of Control for Hyperphosphatemia in Chronic Kidney
Disease Stage 5 Patients
RNF Fall, 2010 Vol. 29 (4)