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Niacin: A Method of Control for Hyperphosphatemia in Chronic Kidney Disease Stage 5 Patients

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This article has been approved for 1.5 CPE units. The online CPEU quiz and certificate of completion can be accessed in the Members Only section of the RPG web site via the My CPEU link. In addition, this CPE offering is available to current RPG members only and the expiration date is November 15, 2011.

Introduction

Hyperphosphatemia is a reoccurring and difficult obstacle to overcome within the Chronic Kidney Disease (CKD) stage 5 population. This condition, most often presenting as part of renal disease, has increased due to the number of individuals with poorly controlled co-morbidities of diabetes, heart disease and hypertension. Left untreated, and with phosphorus (P) levels ranging above 5.5 mg/dL, patients are at risk for a multitude of health issues. These include cardiovascular disease as a result of heart, visceral and peripheral artery calcification, secondary hyperparathyroidism, and advanced bone disease with soft tissue calcification (1). It has been estimated that at least 40 to 50% of all patients undergoing dialysis treatment suffer from some type of renal osteodystrophy (2). Statistically, cardiovascular disease is the number one factor for mortality in renal disease patients (1). Current medical therapies consist of adequate dialysis sessions for removal of P from the bloodstream, a focus on patient education to control dietary intake of P and P binder medications (1). A less researched and newer area of interest is the use of niacin as a method to control hyperphosphatemia. This article will explore current research with niacin used to alleviate hyperphosphatemia in the CKD stage 5 population.

In 2006, the National Kidney Foundation revised the Kidney Disease Outcomes Quality Initiative guidelines to reflect current recommendations for the prevention and treatment of bone and mineral disease. Goal ranges were determined for serum P values and treatment approaches outside of these ranges were discussed for different stages of CKD. CKD stage 5 is one of those stages. It is defined as a glomerular filtration rate of 15 or less with need of hemodialysis or peritoneal dialysis. Within this defined group, it is a goal for P levels to be maintained between 3.5 and 5.5 mg/dL (3). CKD stage 5 typically requires an average P restriction of 800 to 1000 mg per day; with this number varying depending on the amount of protein needed for each individual. If dietary restriction and adequate dialysis are not sufficient for P control, a variety of P binders can be prescribed for improved serum P management (3).

Niacin Reduction of P

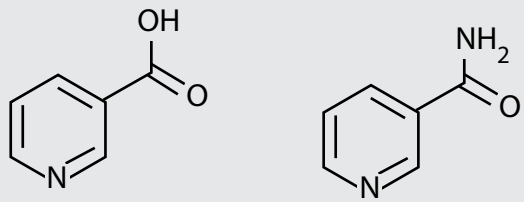
In recent years, research has correlated a

relationship between niacin supplementation and a decrease in high P levels in renal patients. In a healthy individual, the renal tubules are responsible for eliminating excess P from the body. As renal disease progresses and the glomerular filtration rate of the kidneys declines, the normal kidney function of P filtration decreases (4,5). Researchers have been able to identify a transporter within the intestinal and renal tubule lining which is partially responsible for the amount of phosphate absorbed. This transporter, known as type IIb sodium-dependant Pi co-transporter (NaPi-2b), is inhibited by the presence of nicotinamide, and therefore limits the amount of P absorbed when this vitamin is present (4,5).

Different forms of niacin have been studied as to their effect on P blood levels. Niacin is known as nicotinic acid while nicotinamide or niacinamide is the amide of nicotinic acid. The conversion from nicotinic acid to niacinamide is not a direct process. While each is readily absorbed in the body, nicotinic acid is only able to function in the coenzyme forms of nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP) in the cells for the processes of glycogenolysis, fatty acid metabolism and tissue respiration (6). Figure 1 shows the difference in the chemical structures of each.

Both positive and negative side effects of the two different

Figure 1
Chemical Structures of Niacin



Nicotinic Acid (Niacin)

Nicotinamide (Niacinamide)

forms used to control hyperphosphatemia have been identified with niacinamide having less potential harmful side effects. Positive results of use of the nicotinic acid include the decrease of low density lipoprotein cholesterol and an increase in high density lipoprotein (HDL) cholesterol. As cardiovascular disease is the leading cause of death in CKD stage 5 patients, this benefit is recognized as a valuable finding (1). Potential negative side effects of this form include flushing, abnormal liver function tests, thrombocytopenia, an increase in insulin resistance, gastrointestinal disturbances with nausea, vomiting and irritation of pre-existing stomach ulcers, and in rare incidences blurred vision with macular edema (7). With the niacinamide form, most common side effects are gastrointestinal distress and potential thrombocytopenia (7). In studies examining niacin effects, it was found that a dose of aspirin taken before the nicotinic acid can counteract the flushing symptoms (8,9). Conflicting research exists too, in support that liver damage may be caused by administration of niacin. Experts acknowledge that more research is needed, but that timing of the supplement and not exceeding the recommended therapeutic dose of niacin may help to limit liver damage (10). Reaction to this supplementation in diabetic patients also remains controversial. It has been recognized that the benefits on the lipid profile are more valuable than the slight decrease in glucose control (11). Finally, older research is more supportive of niacin causing gastrointestinal upset and blurred vision. More recent research suggests that monitoring patient tolerance and providing lower doses of the supplement cause only minor incidence of these reactions amongst study participants (8,12,13).

Decrease in Hyperphosphatemia with Niacin Supplementation

With understanding of how nicotinamide can inhibit the NaPi-2b transporter within the intestine and renal tubule lining, research has been completed on this aspect of control. A focus has been placed on determining the exact dose of the supplement which can help with P control in the CKD stage 5 patient. Table 1 summarizes each study, the number of participants, duration of trial, and results at the completion of each of the trials.

Six different human clinical studies have identified niacin as a beneficial source in limiting hyperphosphatemia in CKD stage 5 patients. The earliest of these trials examined the serum P values of hemodialysis patients in response to increasing levels of nicotinamide over a three month period of time. Sixty-five individuals were initially given a dose of 500 mg per day of nicotinamide. Every two weeks this dose was increased by 250 mg until P level goals of less than 6.0 mg/dL were obtained (14). Conclusive results indicated that most individuals consumed an average of 1080 mg/day of niacin. With this supplementation, P decreased from 6.9 ± 1.5 mg/dL to 5.4 ± 1.3mg/dL. Being one of the earlier trials focusing on this supplementation, researchers proposed that more trials would be necessary to add validity to their results (14). In a similar study, researchers in India looked at control of hyperphosphatemia while supplementing 34 hemodialysis patients with 375 mg of extended release nicotinic acid daily for eight weeks. Phosphorus levels were measured two weeks into the study and if hyperphosphatemia remained, then the dose was increased to 375 mg nicotinic acid, given twice daily with meals. At the end of the study, average P levels had decreased from 7.7 ± 1.5 mg/dL to 5.6 ± 1 mg/dL (15). Researchers cited failure to consider dietary

P intake, limited number of participants and short trial duration as study limitations (15). In contrast to previous trials, the effect of niacin on P levels was concurrently studied with examination of the effect on HDL levels in a third trial. This particular study included the use of Niaspan, a prolonged release nicotinic acid, (Abbott Laboratories, North Chicago, IL) after a two week washout period from either a calcium or aluminum based P binder. Initially, 20 patients started the study, but only 11 finished due to symptoms of flushing, weight change or hypotension. Participants were given a starting dose of 375 mg per day. Every two weeks, until 12 weeks had passed, this dose was increased to levels of 500, 1000, 1500 or 2000 mg per day depending upon patient tolerance and response in terms of P levels. Results indicated a decrease in average P levels of participants from 7.2 ± 0.7 mg/dL to 5.8 ± 0.75 mg/dL. The average dose needed for P control was 1470 ± 110 mg/day of Niaspan. Along with the lowered P levels, Niaspan supplementation additionally increased HDL levels (16). Authors indicated that future studies determining the relationship of niacin with P and HDL would benefit from a longer trial period and a greater number of study participants (16).

Following these early research trials, three other trials have been completed since 2008 and confirmed similar results as previous studies. In a randomized, double-blind placebo-controlled trial, 33 dialysis patients were subjected to average levels of 500 to 1500 mg per day of niacinamide or to placebo supplementation over an eight week time frame. At the end of the eight weeks, a two week washout period took place. Individuals were then restarted on supplementation for another eight weeks, opposite of what they had been receiving during the initial trial period. Phosphorus levels of the treatment group decreased from 6.26 to 5.47 mg/dL in comparison with the placebo group where levels rose from 5.85 to 5.98 mg/dL (17). Final results again proved that the niacin supplement lowered serum P levels but researchers questioned the potential effects of non-compliance with taking the prescribed supplements as a set back with findings. Additionally, they suggested that an expanded time trial is needed to determine more valid benefits and potential side effects (17). Next, researchers used nicotinic acid supplementation in three hemodialysis and six peritoneal dialysis patients over eight months. Individuals were started on a dose of 500 mg per day of nicotinic acid with this dose increasing to 1000 mg per day by month three. At the start of the study, P levels were measured to be 6.46 ± 0.53 mg/dL. Laboratory values were re-measured at month four and were 4.37 ± 0.63 mg/dL. By the conclusion of the trial, P levels had significantly dropped in all participants and were at levels of 3.94 ± 0.76 mg/dL (18). Researchers found that an average of 1 g/d nicotinic acid was well tolerated amongst the participants (18). Issues that may have affected study conclusions were the limited number of participants and no follow-up period of P measurements after the trial completion. One final study supporting the use of niacin for control of phosphorus levels was completed with 15 peritoneal dialysis patients during an eight week trial period. Seven patients were used as control subjects. The other eight participants were supplemented with 250 mg of niacinamide twice daily. After two weeks, this amount was increased to 500 mg, twice per day. At week four, 750 mg, two times per day, was given. Although this trial's study population was not as large as previous trials with hemodialysis patients, levels of serum P still decreased by approximately 0.7 ± 0.9 mg/dL (19). One major drawback was that only six of the eight supplemented patients completed the trial. Similar to earlier trial conclusions, more participants and a longer trial time frame were recommended to assist with validating the results (19).

Current Methods of P Control

Current methods to combat high P levels in renal patients include adequate dialysis sessions, dietary education and the use of prescribed P binders. A typical hemodialysis patient will complete three sessions per week, ranging from three to five hours depending on patient needs. It is estimated that each dialysis treatment removes approximately 800 mg of P (1). As the typical American consumes more than 1000 mg of P per day with simply meat and dairy intake, it is evident how dialysis alone could be considered deficient for adequate removal of P. For those patients requiring higher protein amounts once on dialysis or consuming foods with hidden P additives, 1000 mg is a low estimate of P intake (1). Malnutrition must be avoided, therefore it is important to prescribe adequate amounts of calories and protein for each individual patient while adhering to P goals (20).

Patient education is another key factor in current methods of controlling hyperphosphatemia. The renal diet is comprised of many other restrictions such as sodium, fluid, calcium, and potassium, making adherence difficult for the patient. Several studies demonstrate the importance of re-educating patients on a regular basis in areas that may not be well understood. In one of the studies, a simple survey consisting of ten questions regarding high P levels, P binders and understanding behind medical treatment of hyperphosphatemia was given to 117 patients. Of the participants, approximately 74% were lacking in dietary education of high P foods. A little over half were unable to demonstrate knowledge about the harmful effects and symptoms of uncontrolled P levels (21). The major finding from this particular study indicated that even with regular counseling related to food and medications, there still remained a barrier between learning the information and applying it in one's lifestyle (21). Two additional research studies

examined the role of more intense dietary education on control of hyperphosphatemia. Both sets of trials concluded that the goal of controlling P could be obtained with regular diet education along with dietary and lifestyle changes (1,22).

Multiple types of P binders exist and are available to be prescribed for P management. Available P binders include: iron containing compounds, aluminum hydroxide, resin-based binders, sevelamer carbonate, calcium-based binders and lanthanum carbonate (4, 5, 18, 23, 24). Each of the binders, while having a positive effect on P control, has its own set of potential drawbacks. Many of the iron containing compounds remain under clinical research to determine a safe dose. Early trials have resulted in diarrhea (5). Aluminum binders are used only under special, short-term conditions due to risk of toxicity, lack of identified safe dose and risk of neurological impairment, osteomalacia and anemia (4,18). Much like the iron containing compounds, resin-based binders remain under clinical investigation. Current trials demonstrate the side effects of constipation and abdominal distention with oral use (5). Of the calcium based binders, sevelamer carbonate and lanthanum carbonate, recommendations vary in regards to which is the most beneficial to be used amongst the renal patient population (23). The calcium based binders, typically calcium acetate or calcium carbonate, may be the most affordable. One problem with these medications is the potential deposit of the calcium and P product in the soft tissues. Experts argue that the expense and quantity of pills needed with the sevelamer carbonate and lanthanum carbonate can contribute more to noncompliance (5,24). A study determining pill burden and adherence to prescribed P binders was undertaken by researchers (25). After data collection from 233 dialysis patients, the mean number of pills taken per day averaged 19, with half or more of these pills being P binders. As the number of pills increased, compliance decreased with an estimate of only 38% of the population studied taking their medications as prescribed (25). Overall, the best method of controlling hyperphosphatemia with P binders remains a very controversial topic and is often determined depending on physician preference. It is apparent that adequate dialysis, dietary compliance and consistent medical therapy each play a major role in maintaining P levels within recommended guidelines.

Discussion/Recommendations for Practice

Based on the reviewed research, it appears that the use of niacinamide to promote P control for CKD stage 5 patients should be considered as an alternative or addition to current therapies of adequate dialysis, dietary education and the existing P binder prescriptions. Non-adherence is one of the largest contributors to hyperphosphatemia within this population. Missing dialysis sessions, dietary consumption of foods that contain evident or added P and not regularly taking prescribed P binders with meals are just a few of the reasons causing hyperphosphatemia and the progression of bone and mineral disease (22). Use of niacinamide may help to reduce this growing problem by decreasing the number of pills being taken. It may also decrease the cost associated with P control methods.

In each of the six reviewed studies, the patients responded well to varying doses of niacin and serum P levels decreased. In the two trials that provided the average amount of niacin needed to maintain goal levels of P, intake fell between the ranges of 1000 mg to 1600 mg per day (14,16). None of the trials provided a maximum dose of more than 2000 mg per day, suggesting that a safe and beneficial dose of niacin supplementation ranges between 1 to 2 grams per day. Careful monitoring of the patient should be of concern when starting a patient on niacin supplementation to determine the individual's personal tolerance level (7). Fewer negative side effects have been found with the niacinamide or extended release nicotinic acid supplementation making these the more recommended forms. Upper limits for intake have been recommended at 35 mg NE for adults 18 years of age and older (26).

Niacin supplementation should not be prescribed to all renal patients. In many of the studies, patients that are pregnant or those with a medical history of liver disease, peptic ulcer disease, gout or cancer were excluded because of the potential for harmful side effects (15,17,18). Minimal symptoms were seen amongst trial participants. This suggests that the preliminary side effects noted with niacin supplementation may not present with the amount of niacin being given or in the time frame of supplementation. Of the symptoms noted with nicotinic acid supplementation, a few individuals were limited by flushing, weight loss, hypotension, diarrhea, thrombocytopenia or a skin rash (15-17). In order to determine the seriousness of these conditions, larger and longer trials are needed to increase knowledge and understanding.

The number of trials determining the effect of either nicotinic acid or niacinamide on hyperphosphatemia is easily the largest limiting factor in this area of research. Each of the six studies evaluated note the importance of future research in determining validity of the results (14-19). Another limitation of the studies included length of the trials. Many of the trials took place over a time frame of two to three months, with only one being completed after eight months. With a short time frame for completion, results could be further validated with a longer trial period. A follow-up measurement of P levels following trial completion would also be of benefit. This would allow researchers to determine if the supplementation was the main factor in decreasing P levels or if other trial influences need to be considered (18). One additional limitation was the number of study participants. The largest num-

Table 1
Summary of Trials Examining Niacin Effect on P Levels

Author(s)	Study Subjects	Study Duration	Results
Takahashi and colleagues	65 hemodialysis patients	12 weeks	Decreased P levels with niacin supplementation
Sampathkumar and colleagues	34 hemodialysis patients	8 weeks	Lower P levels following treatment
Muller and colleagues	19 hemodialysis patients 1 peritoneal dialysis patient	12 weeks	Improvement in P level after supplementation
Cheng and colleagues	33 hemodialysis patients	8 weeks treatment, 2 weeks washout period, 8 weeks placebo	Treatment group saw improvement in P levels. Placebo group had slight increase in P levels.
Valencia and Cruz	3 hemodialysis patients 6 peritoneal patients	8 months	Significant improvement in P levels at 8 months
Young and colleagues	15 hemodialysis patients (8 treatment and 7 control)	8 weeks	Decrease in P levels of treatment group. Increase in P levels of placebo group.

ber of individuals studied was 65 and three of the other five studies were limited to 20 or less participants. Several patients in each of the trials did not complete the full trial. Less disputed results could be obtained in trials with a larger number of participants (14-19).

Strength of study designs were reflected in the outcomes. Each of the trials proved the initial hypothesis that P levels would decrease with the addition of niacin supplementation. The least amount of P improvement was seen in the eight week trial where only six peritoneal patients finished the study (19). A much larger difference was noted in those patient supplemented with nicotinic acid over an eight month time frame (18). Also of original concern, were the side effects of gastrointestinal distress, altered liver function tests and flushing with the nicotinic acid supplementation. Results from the studies were supportive in the fact that many of these symptoms did not appear or were not of significance in a majority of the individuals completing the trials (6).

Due to the limited amount of research on niacin supplementation and control of hyperphosphatemia, future research includes many possibilities. Most needed at this time are longer trials with a larger number of participants to determine the validity of earlier trials. It would also be of interest to determine if niacin effects differ between those on hemodialysis in comparison with those undergoing peritoneal dialysis.

Conclusion

Hyperphosphatemia and bone and mineral disease are ongoing and growing problems amongst patients with CKD stage 5. Until this problem can be better controlled, dialysis patients with chronic hyperphosphatemia will continue to be at an increased risk for mortality from cardiovascular disease. Current therapies of dialysis, education and medications can help decrease this problem. New alternatives such as niacin supplementation should be further researched and examined as to their role and contribution in prevention of hyperphosphatemia and therefore bone and mineral disease. ◆

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