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ORIGINAL ARTICLE

Efficacy and safety of nicotinamide in the management of hyperphosphatemia in pediatric patients on regular hemodialysis

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Abstract
Background Hyperphosphatemia is a common problem in patients with end-stage renal disease (ESRD) who are on maintenance hemodialysis (HD) and contributes to the development of secondary hyperparathyroidism and cardiovascular complications. Nicotinamide (NAM) has been shown in some studies to inhibit intestinal and renal sodium/phosphorus cotransporters and reduce serum phosphorus levels. We have therefore evaluated the efficacy and safety of NAM as adjunctive therapy to calcium-based phosphate binders to control hyperphosphatemia in hemodialysis patients.
Methods Sixty pediatric HD outpatients were randomly divided into two equally sized groups (30 children each). One group received calcium-based phosphate binder (control group), and the other received both the calcium-based phosphate binder + NAM at a dose of 100 mg twice or three times daily (nicotinamide group). Both groups were followed for a 6-month period.
Results Over the 6-month treatment period, children in the NAM group showed a significant decline in the levels of serum phosphorus (p=0.0001), serum calcium–phosphorus (Ca × P; p=0.0001) product and parathyroid hormone (p=0.02) versus baseline values and those of the control group. After 6 months of NAM treatment, the mean serum high-density lipoprotein cholesterol levels had increased significantly (p=0.01), and the median serum triglyceride levels had decreased (p=0.009). There was no significant change in any of these parameters among the children of the control group. The major adverse events associated with the NAM therapy were diarrhea, flushing and nausea.
Conclusion The addition of NAM to therapy with phosphate binders is effective in lowering phosphorus levels and has a beneficial effect on the lipid profile with only mild side effects.

Keywords Pediatric patients · Hemodialysis · Nicotinamide · Hyperphosphatemia · Lipid profile

Introduction

Hyperphosphatemia is a common complication of end-stage renal disease (ESRD) and particularly affects hemodialysis (HD) patients [1]. Elevated serum phosphorus contributes to the development of secondary hyperparathyroidism, renal osteodystrophy and metastatic calcifications [2]. Epidemiological studies have demonstrated a significant association between hyperphosphatemia and increased mortality in ESRD patients, as well as between hyperphosphatemia and increased cardiovascular mortality in and hospitalization of HD patients [2, 3].

In HD patients, serum phosphate levels of>6.5 mg/dl are associated with a significantly increased mortality risk, and similar effects have been reported for the calcium × phosphorus (Ca × P) product (>45.9). An increased Ca × P product is associated with calcium–phosphate precipitation in blood vessels, myocardium and heart valves [4, 5]. The current clinical strategy for management of hyperphosphatemia in HD patients involves: (1) attempts to restrict dietary phosphorus intake; (2) removal of phosphate with three-times-weekly dialysis or (preferred treatment when possible) by daily and/or

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more prolonged dialysis sessions; (3) reduction of intestinal phosphate absorption by the use of binders [6].

Unfortunately, the efficacy of conventional phosphate binders is not reliable, and they are associated with a range of limitations and side effects. Aluminum-containing agents are highly efficient but no longer widely used because of proven neurological, skeletal and hematological toxicity. In addition, magnesium-based binders cause gastrointestinal intolerance [7]. Calcium-based agents have traditionally been used as first-line therapy, since they correct hypocalcemia in addition to reducing serum phosphate levels and are inexpensive. However, these agents may not be suitable for all patients due to dose-limiting hypercalcemia and vascular calcification [8]. Sevelamer was the first non-calcium, aluminum-free agent to be approved for use, but its clinical applications are limited by a large pill burden, metabolic acidosis, gastrointestinal disturbances and high cost; the same is true for lanthanum [9].

A large number of phosphate binders are in clinical development. Within the context of inexpensive phosphate control, nicotinamide (NAM; also referred to as niacinamide) has been studied for its efficacy and safety in reducing serum phosphorus in HD patients, with results suggesting that it may be a useful pharmacological adjuvant to binder-based approaches [10]. NAM is a water-soluble vitamin that is part of the vitamin B complex; both NAM and nicotinic acid (also known as niacin) are forms of vitamin B3 or vitamin PP. Despite their structural similarities and equivalent nutritional properties, NAM and niacin have differing actions and adverse effect profiles. For example, although NAM can cause gastrointestinal discomfort and reportedly lowers platelet counts, it does not cause flushing, which is commonly seen with niacin use [11].

In vitro studies have shown that administration of NAM increases the concentration of nicotinamide adenine dinucleotide (NAD) in renal cortical tissue, which in turn decreases phosphate uptake by inhibiting sodium/phosphorus cotransporters in the rat renal proximal tubule (Na/Pi2a) and intestine (Na/Pi2b) [12–15]. An open-label study of NAM in adult Japanese HD patients who were not taking phosphate binders found that doses of up to 1750 mg/day decreased serum phosphorus from 6.9 to 5.4 mg/dl [16]. In addition, the levels of high-density lipoprotein (HDL) cholesterol increased and those of low-density lipoprotein (LDL) cholesterol declined during the 12-week-treatment period [16].

Pediatric HD patients in Egypt receive relatively poor phosphorus control and might benefit from the addition of NAM to their binder regimen. This study was undertaken to evaluate the efficacy and safety of NAM as an adjunctive therapy to calcium-based phosphate binders in the treatment of hyperphosphatemia among ESRD pediatric patients on regular HD.

Methods

This was a prospective, simply randomized, open label, controlled study conducted on pediatric patients with ESRD who were undergoing HD at the Pediatric Nephrology and Dialysis Unit, Ain Shams University Children's Hospital from December 2013 to June 2014. A review of previous studies on changes in phosphorus revealed that the mean difference and the standard deviation (SD) were nearly equal and that at a significance level of 0.05 and power of 90 %, a sample size of 44 children (22 in each group) would be required. To be included in the study the patient had to be between the ages of 6 and 18 years, to have been on regular HD for ≥3 months at entry at a frequency of ≥3 times weekly, to have been receiving a stable phosphate binder dose for at least 1 month at screening and to have a serum phosphate level of>5 mg/dl. Patients with peptic ulcers, serious liver damage, poorly controlled diabetes, uncontrolled high blood pressure, and thrombocytopenia were excluded from the study, as were noncompliant patients, patients currently taking Cinacalcet, patients with a previous intolerance to either niacin or NAM and those awaiting a surgical procedure within the upcoming 6 months.

The HD regimen of all patients typically consisted of HD sessions of 3–4 h, 3 days per week. Sixty eligible patients were randomized to two groups of equal size (n = 30). The 30 patients in the control group received a calcium-based phosphate binder (calcium acetate or calcium carbonate) at a dose of 500 mg, two to three times daily for 6 months. The 30 patients of the nicotinamide (NAM) group received the same calcium-based phosphate binder, also at a dose of 500 mg, two to three times daily, + a NAM tablet for 6 months.

NAM dosing and safety points

Nicotinamide tablets (100 mg) were purchased from Holland & Barrett Retail Ltd., Nuneaton, Warwickshire, UK). They were administered at a dose of 100 mg twice daily if serum phosphorus levels were ≥5 and ≤8 mg and at a dose of 100 mg three times daily if the serum phosphorus levels were >8 mg. The dosage was decreased to 100 mg once daily when the serum phosphorus level was <3.0 mg/dl. Within the study guidelines, a decrease in phosphate binder dosage was permitted when the serum phosphorus level remained at <3.0 mg/dl despite a decrease in the dosage of NAM. An increase in phosphate binder dosage, in conjunction with dietary counseling, was permitted when two consecutive phosphorus levels were >7.0 mg/dl or the Ca × P product was >70 mg^2/dl^2.

Nutritional counseling was provided to patients and caregivers of all children enrolled in the study to limit the intake of diets rich in phosphorous. The advice given was to limit protein intake to about 1.0 g/kg/day, increase the proportion of plant-derived foods as sources of protein since their

phosphorus content is less absorbed and to restrict the consumption of highly processed fast foods.

Each patient was subjected to a full medical history assessment and clinical examination to ensure the absence of exclusion criteria. Biochemical parameters were analyzed by standard clinical laboratory measures. Serum phosphorus and calcium levels were estimated at baseline and at the third and sixth month time-points, before the HD session. Laboratory tests for complete blood count, blood sugar, parathyroid hormone (PTH), lipid profile, renal profile and liver function were performed at baseline and at the end of the study. Patients were regularly monitored for adverse side effects, such as gastrointestinal discomfort, during the study period.

Statistical analysis

Statistical analysis was performed using the SPSS statistical program (v.20; IBM Corp., Armonk, NY). Data were expressed as the median and interquartile range for quantitative non-parametric measurements, as the mean and SD for parametric data and as numbers and percentages for categorical data. The paired Student *t* test, unpaired Student *t* test, one-way repeated measure analysis of variance (ANOVA), Mann–Whitney test, Wilcoxon test and chi-square test were used for data analysis. A probability of error of <0.05 was considered to be significant and <0.001 to be highly significant.

Results

A total of 60 pediatric patients with ESRD on regular HD were enrolled, and all completed the current study. Among those in the NAM group, 20 patients received NAM at a dose of 100 mg twice daily, as their serum phosphorus level was ≥5 and ≤8 mg, and 10 patients received NAM at a dose of 100 mg three times daily as their serum phosphorus level was >8 mg. There was no need to change either the dose of phosphate binders or NAM during the study period. At baseline, there was no significant difference between the groups in terms of demographics, clinical characteristics or laboratory and clinical parameters (Tables 1, 2).

Drug efficacy

The one-way repeated measure ANOVA revealed that both mean serum phosphorus level (Fig. 1) and Ca × P product level significantly decreased (both $p=0.0001$) over time from baseline to 3 and 6 months, in children in the NAM group. No significant change ($p>0.05$) was observed in mean serum

Table 1 Baseline demographics and clinical characteristics of the two patient groups

Baseline evaluation	Control group ($n=30$)	Nicotinamide group ($n=30$)	p value[a]
Demographic data			
Age	11.3±3 (7–17)	11.9±2.9 (7–17)	0.397
Sex			
Male	17 (58 %)	16 (53.3 %)	0.068
Female	13 (42 %)	14 (46.7 %)	
Weight	25.1±4.9	26.2±7.9	0.539
Clinical characteristics			
Cause of ESRD			
Chronic nephritic syndrome	7 (23.3 %)	8 (26.6 %)	0.83
Interstitial nephritis	7 (23.3 %)	4 (13.3 %)	
Lupus nephritis	6 (20 %)	5 (16.6 %)	
Chronic tubulointersitial nephritis	3 (10 %)	5 (16.6 %)	
Obstructive uropathy	1 (3.3 %)	2 (6.6 %)	
Polycystic kidney	4 (13.3 %)	3 (10 %)	
Vesicouretric reflux	2 (6.6 %)	3 (10 %)	
Comorbidities associated with renal disease			
Hypertension	23 (76.6 %)	21 (70 %)	0.76
Congestive heart failure	3 (10 %)	5 (16.6 %)	
Heart burn	4 (13.3 %)	4 (13.3 %)	

Data are presented as the mean ± standard deviation (SD) with the range in parenthesis or as a number with the percentage in parenthesis, as appropriate

ESRD, End-stage renal disease, *n* number of patients

[a] At baseline, there was no (highly) significant difference [($p\leq0.001$) $p\leq0.05$] between the groups in terms of demographics, and clinical characteristics

Table 2 Baseline laboratory parameters of the two patient groups

Baseline evaluation	Control group (n=30)	Nicotinamide group (n=30)	p[a]
Creatinine (mg/dl)[b]	8.7±2.4	9.2±1.8	0.346
Blood urea nitrogen (mg/dl)[b]	142.7±43.4	158.5±38.6	0.146
Uric acid (mg/dl)[b]	7.6±1.3	7.1±1.4	0.097
White blood cell ($\times 10^9$ cells/l)[b]	5.4±1.4	6.3±2	0.074
Hemoglobin (g/dl)[b]	9.8±1.9	10±1.7	0.662
Platelets ($\times 10^9$/l)[b]	202.6±71.9	213.9±85.7	0.58
Calcium (mg/dl)[b]	9.3±1.7	8.7±1.6	0.086
Phosphorus (mg/dl)[b]	7.7±1.9	6.9±1.6	0.108
Ca × P (mg^2/dl^2)[b]	68.8±23.9	58.8±21.3	0.098
Parathyroid hormone (μg/dl)[c]	231±615	339±516	0.862
Alkaline phosphatase (U/l)[c]	191±218	242±310	0.649
Aspartate aminotransferase (U/l)[b]	29.4±17.6	20.4±4.1	0.068
Alanine aminotransferase (U/l)[c]	19±13	15±6	0.084
LDL (mg/dl)[b]	91.9±29.5	98.9±29.9	0.367
HDL (mg/dl)[b]	36.8±9.1	36.2±6.9	0.79
Total cholesterol (mg/dl)[c]	127±57	164.5±57	0.167
Total triglycerides (mg/dl)[c]	110±50	148.5±96	0.058
Blood glucose level (mg/dl)[c]	90±9	89.5±11	0.528
Total Kt/V	2.4±0.67	1.95±0.24	0.12

Ca × P, calcium × phosphorus product; LDL, low-density lipoprotein; HDL, high-density lipoprotein

[a] At baseline, there was no (highly) significant difference [($p \leq 0.001$) $p \leq 0.05$] between the groups in terms of laboratory parameters

[b] Data expressed as mean±SD

[c] Data expressed as median±interquartile range

calcium over time. In contrast, the children in the control group showed a significant increase in mean serum phosphorus (p=0.0013) and Ca × P product (p=0.0011) over time from baseline to 3 and 6 months. No significant change (p>0.05) was observed in the mean serum calcium over time (Tables 3, 4).

The unpaired Student t-test revealed that there were no significant differences (p>0.05) in the mean serum calcium level between the control and NAM groups, but that there were highly significant differences (p=0.0011) between the groups for the mean serum phosphorus and serum Ca × P product (p=0.0012) levels.

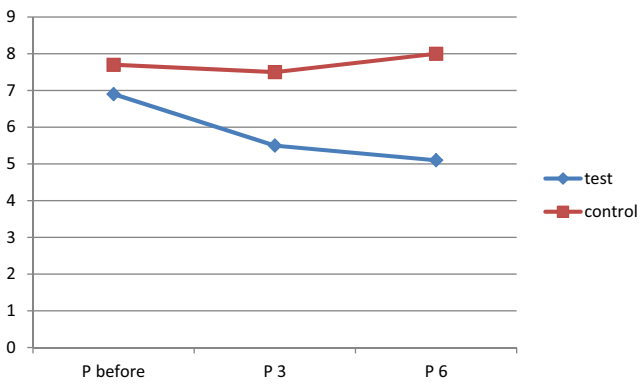

Fig. 1 Mean serum level of phosphorus (in mg/dl) at baseline (*P before*) and at 3 (*P 3*) and 6 (*P 6*) months after initiating treatment in the control and nicotinamide (test) groups

Pairwise comparisons using Bonferroni adjustment showed a highly significant difference in serum phosphorus and serum Ca × P product levels in the NAM group at the following time points: between baseline and month 3 of the study period (p=0.0001); between baseline and month 6 of the study period (p=0.0001); between months 3 and 6 of the study period (p=0.001). In the control group, serum phosphorus levels were signficantly different between months 3 and 6 of the study period, and the serum Ca × P product levels were significantly different between baseline and month 6 of the study period (Tables 3, 4).

In children receiving the NAM treatment, median serum PTH levels decreased from 339 ± 516 μg/dl at baseline to 290 ± 467 μg/dl at the end of the study (treatment month 6) (p = 0.02); mean serum (HDL) cholesterol levels increased from 36.2 ± 6.9 mg/dl at baseline to 39.8 ± 3.8 mg/dl (p = 0.01) by the end of the study. In addition, median serum triglyceride (TG) levels decreased from 148.5±96 mg/dL at baseline to 127.5±80 (p=0.009) at the end of the study. In the control group, there were no significant differences between median serum PTH, mean serum HDL and median serum TG levels and their respective values at the end of the

Table 3 Serum level of calcium, phosphorus and calcium × phosphorus product in the nicotinamide group at baseline and at months 3 and 6 after treatment initiation

Variable	Serum level			Overall *p* value	Bonferroni pairwise comparison (*p* value)		
	Baseline	Month 3	Month 6		Month 3 to baseline	Month 6 to baseline	Month 3 to month 6
Calcium (mg/dl)	8.7±1.6	9±1.6	9.3±1.5	0.08	NS	NS	NS
Phosphorus (mg/dl)	6.9±1.6	5.5±1.3	5.1±0.9	0.0001**	0.0001**	0.0001**	0.001**
Ca × P (mg^2/dl^2)	58.8±21.3	50.5±17.5	47.8±14.4	0.0001**	0.001**	0.0001**	NS

NS, Non-significant; *significant at $p \leq 0.05$) **high significant at $p \leq 0.001$; Ca × P, calcium × phosphorus product

Data are presented as the mean±SD

study. There were no changes in serum total cholesterol levels or in serum LDL levels in the NAM group throughout the study period, as well as no significant changes in other laboratory values during NAM treatment. There were also no significant differences between the two study groups for any of the other laboratory parameters.

Adverse events

During the 6 months of the study, the following adverse events were reported in 20 patients of the NAM (test) group: diarrhea, nausea, vomiting and flushing (Fig. 2). None of the patients in the NAM group discontinued the study due to any of these adverse events, and all adverse events reported were resolved after withdrawal of the NAM.

At the end of the study there were no significant differences ($p>0.05$) between the NAM and control groups in either liver function [aspartate transaminase (AST), alanine transaminase (ALT)] or kidney function (creatinine, blood urea nitrogen, uric acid).

In terms of platelets, the NAM group showed a significant ($p=0.014$) decrease in mean platelet count from 213.9±85.7× 10^9/l at baseline, reaching 191.4±69.7×10^9/l at the end of the 6-month study period, but the level remained within the normal range, and none of the patients experienced any bleeding events during the study. The control group showed no significant difference in platelet count at the end of the study period compared to baseline values.

Discussion

Nicotinamide is a component of NAD, a coenzyme involved in many cellular oxidative reduction reactions. It has been suggested that NAD is an intracellular inhibitor of sodium-dependent phosphate transport. In rat models, NAM has been shown to increase the renal cortical NAD concentration, to inhibit phosphate uptake by brush border membrane vesicles of renal proximal tubules in the kidney and to increase phosphate excretion in thyroparathyroidectomized rats [17]. NAM 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 ESRD. As a result, there is solid experimental evidence that NAM decreases phosphorus levels in HD patients [12–16, 18–23].

According to our knowledge our study is the first to assess the efficacy and safety of NAM on phosphorus reduction in conjunction with phosphate binders in pediatric patients. We observed that the administration of oral NAM to our pediatric patients substantially reduced serum phosphorus and Ca × P product levels within a 6-month treatment period. In the NAM group, the decrease in mean serum phosphorus levels was highly significant ($p=0.0001$): from 6.9±1.6 mg/dl at baseline to 5.5±1.3 at month 3 of treatment to 5.1±0.9 mg/dl at the end of month 6 (end of study). A highly significant decrease ($p=0.0001$) in mean Ca × P product was also achieved in the NAM group: from 58.8±21.3 mg^2/dl^2 at baseline to 50.5±17.5 mg^2/dl^2 at month 3 of treatment to 47.8±14.4 mg^2/dl^2 at the end of month 6.

Table 4 Serum level of calcium, phosphorus and Ca × P product in the control group at baseline and at months 3 and 6 after treatment initiation

Variable	Serum level			Overall *p* value	Bonferroni pairwise comparison (*p* value)		
	Baseline	Month 3	Month 6		Month 3 to baseline	Month 6 to baseline	Month 3 to month 6
Calcium (mg/dl)	9.3±1.7	9.2±1.7	9.5±1.3	0.13	NS	NS	NS
Phosphorus (mg/dl)	7.7±1.9	7.8±1.4	8.1±1.4	0.0001**	NS	NS	0.01*
Ca × P (mg^2/dl^2)	68.8±23.9	70.8±15.9	76.1±17.7	0.0001**	NS	0.03*	NS

NS, Non-significant; *significant at $p \leq 0.05$) **high significant at $p \leq 0.001$; Ca × P, calcium × phosphorus product

Data expressed as mean±SD

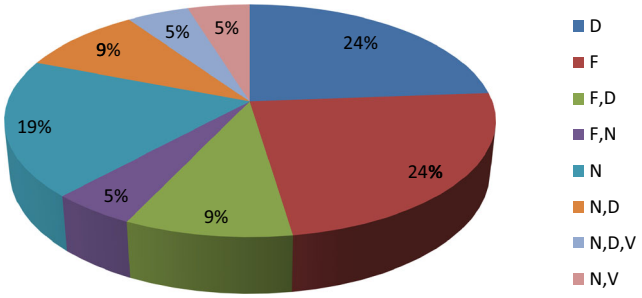

Fig. 2 Percentage of adverse events reported by patients in the nicotinamide group. *D* Diarrhea, *N* nausea, *V* vomiting, *F* flushing

In our study, we co-administered NAM with calcium-based phosphate binders with the aim to additively reduce the phosphate levels. Our results correlate with those reported by Cheng et al. [19] and Young et al. [20] which demonstrated that NAM lowers serum phosphorus levels in maintenance HD patients when co-administered with other phosphate binders. On the other hand, Takahashi et al. [16], Sampathkumar et al. [21] and Vasantha et al. [22] reported that NAM reduces serum phosphorus even when traditional binding agents were withheld.

In our study, with NAM treatment the median serum PTH levels decreased significantly by the end of the study (p=0.02), while the control group showed no significant change compared to baseline levels. These findings are in accordance with those of Takahashi et al. [16] who reported median serum PTH levels of 230 μg/dl at treatment week 4 which declined to 150 μg/dl by the end of the 12-week treatment period (p<0.05). On the contrary, Cheng et al. [19] and Shahbazian et al. [23] found no significant change in serum PTH levels. The discrepancy between our results and those of previous studies can possibly be attributed to the relatively longer duration of our study.

Takahashi et al. [16] reported that NAM raised the HDL level from 47 to 67 mg/dl (p<0.0001) and lowered the LDL level from 79 to 70 mg/dl (p<0.01) in Japanese patients on HD. In our study, NAM treatment resulted in a significant increase in the mean serum HDL level (p=0.03) and a significant decrease in the median serum TG level (p=0.009), but it had no effect on LDL level. Cheng et al. [19] reported similar results, with an increase in HDL level of 11 mg/dl (21.5 % increase) in patients receiving NAM treatment, but no decrease in LDL values. NAM has been reported to decrease the levels of plasma fatty acids, TG and LDL by reducing lipase effects in adipose tissue and to presumably increase HDL concentration by increasing apoA-1, which is the main lipoprotein of HDL [19].

We found no significant change in uric acid levels in the NAM group as compared to the control group at the end of the study. This is in accordance with results from several other studies which also showed no effect of NAM on uric acid levels [19, 21, 23, 24].

During the 6-month period of our study, none of the patients suffered hepatotoxicity or any significant changes in liver function tests (ALT, AST), possibly due to the use of NAM at a low dose and for a short duration. It has, however, been reported that nicotinic acid or NAM at higher doses (>3 g/day) can cause frequent liver enzyme abnormalities and cases of hepatotoxicity [25].

Most previous studies evaluated the effect of NAM on hyperphosphatemia in HD patients and disregarded its effect on hemoglobin level [16, 19]. However, a trend towards reduced mean hemoglobin in the NAM treatment group was demonstrated by Young et al. [20]. In our study, however, the difference in hemoglobin levels between the NAM and control groups was not significant.

In terms of the adverse drug reactions of NAM, thrombocytopenia has been a concern from previous studies. We observed a significant decrease (p=0.014) in the mean platelet count in the NAM group, yet it did remain within the normal acceptable range, and none of the patients experienced any bleeding events. On the contrary, Rottembourg et al. evaluated six dialysis patients being treated with NAM 1000 mg/day and reported the development of significant thrombocytopenia within 3 months of treatment initiation [26]. In their study, Shahbazian et al. showed a decline in the mean platelet count from $216.46 \pm 64.8 \times 10^9$/l at baseline to $168.79 \pm 57.1 \times 10^9$/l at the end of the study. The mechanism underlying this adverse effect has not yet been clearly elucidated; one suggestion is that thrombocytopenia might result from the low levels of thyroxin-binding globulin induced by NAM and its derivatives [23].

Eight cases of flushing were reported in our study during the second month of the NAM treatment; all cases resolved spontaneously in the third month, with no need to stop NAM treatment. Cheng et al. [19] and Young et al. [20] reported only one case of abdominal rash and another case of pruritic rash, respectively. In both studies none of the patients randomized to the NAM treatment developed flushing. The variations in the reported frequencies of the different adverse effects may be attributed to differences in the age of patients and treatment duration between our study and these other studies.

NAM has been reported to be well tolerated in the general population [27]. The percentages of gastrointestinal disturbances (nausea, vomiting and diarrhea) among our patients receiving NAM were 30 % (9/30), 6.67 % (2/30) and 33.3 % (10/30), respectively. Similarly, in an open-label study, Delanaye et al. reported that five of the six patients receiving NAM developed diarrhea; the symptoms emerged at a mean dose of 1050 (±447 SD) mg/day and resolved after withdrawal of the drug [28]. These researchers pointed out that all of the patients were also taking calcium binders and/or sevelamer, which may have contributed to the occurrence of these adverse events. Similar findings have been reported by Takahashi et al. [16] and Young et al. [20].

Our study has a number of limitations, such as being an open label study, having a small number of cases, not measuring serum NAD concentrations and not measuring serum calcium, phosphorus and Ca × P product monthly due to financial constraints.

Conclusion

Although hyperphosphatemia is not yet an approved indication for NAM, recent clinical studies and the results of our randomized, open label, controlled study demonstrate that NAM is safe and effective in controlling serum phosphorus when co-administered with phosphate binders in pediatric patients on HD. In addition, NAM increased serum HDL levels and decreased TG levels. The combination of lowering phosphorus with a beneficial change in lipid profiles makes NAM an attractive agent for further investigation and an interesting adjuvant to phosphate binders for the treatment of hyperphosphatemia in pediatric patients on regular HD.

Additional, large-scale, multicenter, randomized, double-blinded placebo-controlled trials of longer duration are warranted to further evaluate the phosphorus-lowering efficacy of NAM and critically examine the safety profile of this promising therapy.

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Compliance with ethical standards

The study protocol was revised and approved by the ethics committee of the Faculty of Pharmacy, Ain Shams University. The study was performed in accordance with the Declaration of Helsinki. Prior to participation all caregivers of eligible children were informed about the study protocol and signed a written informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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