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ORIGINAL ARTICLE

Observational Study

Bicarbonate levels in hemodialysis patients switching from lanthanum carbonate to sucroferric oxyhydroxide

Aristeidis Stavroulopoulos, Vasiliki Aresti, Christoforos Papadopoulos, Panagiotis Nennes, Polixeni Metaxaki, Anastasios Galinas

Aristeidis Stavroulopoulos, Vasiliki Aresti, Christoforos Papadopoulos, Panagiotis Nennes, Polixeni Metaxaki, Anastasios Galinas, Department of Nephrology, IASIO Hospital, General Clinic of Kallithea, Athens 17676, Greece

ORCID number: Aristeidis Stavroulopoulos (0000-0002-1368-5892); Vasiliki Aresti (0000-0002-9741-9005); Christoforos Papadopoulos (0000-0002-4370-6084); Panagiotis Nennes (0000-0003-1760-3302); Polixeni Metaxaki (0000-0003-0107-3431); Anastasios Galinas (0000-0002-0566-8558).

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Correspondence to: Aristeidis Stavroulopoulos, BM BCh, MD, Chief Doctor, Doctor, Department of Nephrology, IASIO Hospital, General Clinic of Kallithea, Sivitanidou 36, Athens 17676, Greece. stavoulopoulos@yahoo.co.uk
Telephone: +30-69-47824197
Fax: +30-21-09583722

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Abstract

AIM

To examine possible alterations in acid-base parameters in patients switching from lanthanum carbonate (LanC) to sucroferric oxyhydroxide (SFOH).

METHODS

Fifteen stable hemodialysis patients were switched from LanC to SFOH. Only nine continued on SFOH, three returned to LanC and the other three switched to sevelamer carbonate. The later six patients served as a control group to the SFOH group of nine patients. Blood was sampled on the 3-d and the last 2-d interval of the week prior to switching and six weeks after. Bicarbonate levels (HCO_3^-), pH, pO_2, pCO_2 were measured, and the mean of the two measurements (3-d and 2-d interval) was calculated.

RESULTS

Comparing pre-switching to post-switching measurements

in the SFOH group, no statistically significant differences were found in any of the parameters studied. The mean pre-switching HCO_3^- was 22.41 ± 1.66 mmol/L and the mean post-switching was 22.62 ± 2.25 mmol/L (P = 0.889). Respectively, the mean pH= 7.38 ± 0.03 *vs* 7.39 ± 0.03 (P = 0.635), mean pCO_2= 38.41 ± 3.29 *vs* 38.37 ± 3.62 mmHg (P = 0.767), and Phosphate = 1.57 ± 0.27 *vs* 1.36 ± 0.38mmol/L (P = 0.214). There were not any significant differences when we performed the same analyses in the control group or between the SFOH group and control group. No correlations were found, either between pre-switching LanC daily dose or between post-switching daily dose of the new binder and the measured parameters.

CONCLUSION

In our small study, switching from LanC to SFOH did not have any significant effect on blood bicarbonate levels and gas analysis, indicating that there is no need to change hemodialysis prescription regarding these parameters.

Key words: Gas analysis; Hemodialysis; Lanthanum carbonate; Acidosis; Bicarbonate; Phosphate binder; Sucroferric oxyhydroxide

Core tip: Phosphate binders used for the control of hyperphosphatemia contribute to acid-base balance through their effect on serum phosphate and through the effect of the binders' constituents that have alkaline or acidic properties. This is the first study showing that switching from Lanthanum Carbonate to the novel phosphate binder sucroferric oxyhydroxide did not have any significant effect on blood bicarbonate levels and gas analysis. Thus, there is no need to change hemodialysis prescription regarding these parameters.

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INTRODUCTION

Metabolic acidosis is a characteristic complication of end stage kidney disease (ESKD) and is associated with major systemic effects and increased mortality[1,2]. Hyperphosphatemia, another common complication of ESKD, partially contributes to metabolic acidosis and affects the acid-base status of the patients[1]. Phosphate binders used for control of hyperphoshatemia contribute to acid-base balance through their effect on serum phosphate and through the effect of the binders' constituents that have alkaline or acidic properties[3]. The most characteristic is the case of sevelamer hydrochloride (SevH), which is associated with dose-dependent aggravation of metabolic acidosis in ESKD patients due to its hydrochloride content[4,5]. This acidosis is ameliorated after switching to sevelamer carbonate (SevC) or other phosphate binders with alkaline content, such as calcium carbonate (CalC) or lanthanum carbonate (LanC)[6-9]. However, despite the above mentioned studies, a recent meta-analysis suggests that the effect of phosphate binders in clinically important outcomes, such as metabolic acidosis, remains understudied[10].

Sucroferric oxyhydroxide (SFOH) is a polynuclear iron(III)-oxyhydroxide-based phosphate binder recently approved for the treatment of hyperphosphatemia in patients with ESKD. It is a safe and potent phosphate binder with increasing use among hemodialysis patients, both as an initial treatment choice or as an alternative when other binders fail[11,12]. However, little is known regarding the influence of this novel binder on the acid-base status of hemodialysis patients. Aim of our study was to examine possible alterations in acid-base parameters in hemodialysis patients switching from LanC to SFOH.

MATERIALS AND METHODS

Study population

We prospectively evaluated 15 clinically stable, Caucasian, anuric patients from the same unit who switched from LanC to SFOH (Table 1). The patients were taking LanC in the form of 750 mg chewable pills (Fosrenol, Shire Pharmaceuticals Cont. Ltd, United Kingdom) for at least 6 mo, but they had to change phosphate binder due to logistic reasons (disposal and access to the drug limitations). The new binder SFOH (Velphoro, Vifor Fresenius Medical Care Renal Pharma Ltd) was chosen as it is chewable with low pill burden, like LanC. SFOH pills of 500 mg were gradually introduced and titrated within two weeks to a maintenance dose. However, only nine continued on the new binder. The main reasons for discontinuation were gastrointestinal symptoms and taste of the product; thus, three patients returned to LanC and the rest switched to SevC. Therefore, we decided to use these six patients as a control group to the SFOH group of nine patients. No significant differences in the basic characteristics (age, gender, ESKD cause, dialysis vintage, Kt/V, dialysis modality) existed between the two groups. All patients were dialyzed using polysulphone membranes with 1.8-2 m^2 surface area, blood flow rate of 300-350 mL/min, and dialysate flow rate of 600 mL/min. Fifty-percent of them were on online hemodiafiltration. All patients had a well-functioning vascular access and dialyzed adequately within the recommended targets (12 h weekly, spKt/V = 1.32-2.14). Dialysis fluid had the following composition:

Table 1 Baseline characteristics of the study population (n = 15)

	SFOH group, n = 9	Control group, n = 6	P value
Age (yr)	78 (35-90)	73 (49-91)	NS
Male/Female	9/0	4/2	NS
Cause of ESKD	4 DM, 2 GN, 2 UN, 1 ADPKD	2 DM, 2 HN, 1 GN, 1 UN	NS
Dialysis vintage (mo)	53 (19-131)	49 (21-67)	NS
Arteriovenous fistula/Graft	6/3	4/2	NS
Single pool Kt/V	1.56 ± 0.16	1.57 ± 0.29	NS
Dose of LanC pre switching (mg/d)	2250 (750-3000)	3000 (1500-3750)	NS
Number of LanC pills pre switching	3 (1-4)	4 (2-5)	NS
Calcium carbonate: *n*, dose (mg/d)	1, 750	1, 1250	NS
Cinacalcet: *n*, dose (mg/d)	1, 60	1, 30	NS
Paricalcitol: *n*, dose (mcg/wk)	6, 10 (7.5-15)	4, 5 (5-10)	NS

ADPKD: Adult dominant polycystic kidney disease; DM: Diabetes mellitus; ESKD: End stage kidney disease; GN: Glomerulonephritis; HN: Hypertensive nephrosclerosis; LanC: Lanthanum carbonate; NS: Non-significant; SFOH: Sucroferric oxyhydroxide.

Sodium: 138 mmol/L, Potassium: 2.0 mmol/L, Calcium: 1.25-1.75 mmol/L, Magnesium: 0.5 mmol/L, Chloride: 108.5-109.5 mmol/L, Acetate: 3 mmol/L, Bicarbonate: 32 mmol/L, and Glucose: 5.55 mmol/L. Dialysate composition and doses of vitamin D analogs, cinacalcet and CalC, as well as hemodialysis prescription (including bicarbonate conductivity), remained unchanged throughout the study for each patient. Ultrafiltration rates were adjusted to the individual needs of the patients. Dietary consultation regarding phosphorus, potassium and protein intake was the same before and during the study. The study was performed in accordance with the Declaration of Helsinki and with the approval of the hospital ethics committee. Informed written consent was obtained from all patients before they entered the study.

Blood analysis

Blood was sampled from the "arterial needle" of the vascular access in all studied patients before dialysis sessions. Samples were collected on the 3-d and the last 2-d interdialytic interval of the week prior to switching (Baseline) and six weeks after at the same intervals. Whole blood pH, pO_2, pCO_2, bicarbonate levels (HCO_3^-), base excess (BE) and potassium (K^+) were measured using a Cobas B221 blood gas analyzer (Roche Diagnostics Limited, CH-6343 Rotkreuz, Switzerland). Serum phosphate levels were measured the same days using standard laboratory methods. The arithmetic mean (average) of the two pre-switching (baseline) measurements (2 and 3-d interdialytic interval) and the respective mean of the two post-switching measurements (6 wk) were also calculated for each of the above mentioned parameters.

Statistical analysis

All data are presented as mean ± SD and median with (minimum-maximum), according to the distribution. Due to the small sample size, non-parametric tests were used. Differences in parameters between studied groups of patients were analyzed using the Wilcoxon signed-rank test for paired samples and the Mann-Whitney U test for independent samples. Bivariate correlations were performed using Spearman's rank correlation analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Patients who switched to SFOH (SFOH group) had an effective phosphate control (Table 2), without increasing the pill burden, [number of LanC pills: 3 (1-4) *vs* SFOH pills: 2 (1-6), P = 0.849]. Comparing the mean values of the measured acid-base balance parameters, pre- and post-switching, no difference was found in any of them (Table 2). No statistically significant differences were found even when we analyzed the data for the 3-d and the 2-d interdialytic intervals separately (Supplementary Tables 1 and 2), or when we performed the same analyses in the control group or between the two groups (data not shown).

No correlations were found, either between pre-switching daily LanC dose and the measured parameters, or between post-switching daily dose of the new binder and the measured parameters (data not shown).

The only significant differences that we found were between the 3-d and 2-d measurements. HCO_3^-, BE, and pH were significantly lower and K^+ was higher at the 3-d *vs* 2-d interdialytic interval, as expected. For example, in the whole group of patients, baseline 3-d HCO_3^- were 21.2 ± 2.17 mmol/L, BE: -3.5 (-4.8 to-2.3) mmol/L, pH: 7.373 ± 0.031, and K^+: 4.69 ± 0.46 mmol/L. Respective values for the baseline 2-d interval were: HCO_3^-: 22.53 ± 2.68 mmol/L (P = 0.005, comparing to 3-d), BE: -2.2 (-3.3 to -0.4) mmol/L (P = 0.001), pH 7.389 ± 0.029 (P = 0.003) and K^+ 4.29 ± 0.42 mmol/L (P = 0.04). Accordingly, 3-d pCO_2 was lower (37.2 ± 3.34 mmHg) *vs* 2-d (38.19 ± 4.51 mmHg), however the difference did not reach statistical significance (P = 0.061). Phosphate levels were the same, 1.42 ± 0.4 mmol/L *vs* 1.46 ± 0.26 mmol/L (P = 0.801), indicating that phosphate binders are effective in maintaining stable phosphate levels all days. When we performed the same analyses in the post-switching

Table 2 Paired comparisons, pre- and post-switching in the two groups

	SFOH group, *n* = 9			Control group, *n* = 6		
	Baseline	6 wk	*P* value	Baseline	6 wk	*P* value
HCO_3^- (mmol/L)	22.41 ± 1.66	22.62 ± 2.25	0.889	21.05 ± 3.14	21.12 ± 2.27	0.917
pH	7.38 ± 0.03	7.39 ± 0.03	0.635	7.37 ± 0.033	7.36 ± 0.019	0.917
pCO_2 (mmHg)	38.41 ± 3.29	38.37 ± 3.62	0.767	36.62 ± 4.55	37.82 ± 4.97	0.173
pO_2 (mmHg)	93.1 ± 12.04	97.4 ± 10.08	0.953	82.8 ± 11.47	79.9 ± 14.35	0.463
BE (mmol/L)	-2.55 (-3.8 to -0.98)	-2.9 (-3.92 to -0.22)	0.722	-3.27 (-5.6 to -2.1)	-3.85 (-5.5 to -2)	0.917
K^+ (mmol/L)	4.47 ± 0.32	4.38 ± 0.64	0.678	4.52 ± 0.23	4.6 ± 0.23	0.600
Phosphate (mmol/L)	1.57 ± 0.27	1.36 ± 0.38	0.214	1.34 ± 0.33	1.57 ± 0.48	0.249

The laboratory values refer to the average of the respective 2- and 3-d interdialytic interval and are expressed as mean ± SD or as median (min.-max.), *P* value denotes in group comparison (Wilcoxon signed rank test). SFOH: Sucroferric oxyhydroxide; BE: Base excess.

measurements or in the different groups, the findings were similar (data not shown).

DISCUSSION

In our study, we found that when hemodialysis patients are switching from LanC to SFOH, despite the loss of carbonate provided by LanC, there is no significant consequence on acid-base balance. Several explanations may exist for this finding. First, the iron oxide hydroxide binds phosphate in the gastrointestinal tract through a direct ionic interaction between the negatively charged oxygen ions on the phosphate and the ferric ions in the ferric oxide, forming $FePO_4$[13]. During this interaction, hydroxyl groups are released[13], indicating that SFOH acts as a base. An additional explanation could be that the effect of the alkali contained in LanC is small and its loss is compensated by endogenous adaption from blood and bone buffering and residual renal function, when present. This may be particularly true when doses of LanC are not very high or when there is no severe acidosis, like in our patients. There was only one prospective study found where LanC was introduced in phosphate binder-naïve patients. There, serum bicarbonate levels remained stable after 9 mo of LanC in 28 patients with moderate CKD (21.9 ± 2.9 mmol/L at baseline *vs* 21.8 ± 2.4 mmol/L at 9 mo), indicating that the effect of the carbonate is small[14]. Furthermore, it is well known that switching to LanC can ameliorate the acidosis caused by SevH[7,8]. However, this may not be the result of the alkalinizing agent of LanC, but rather the consequence of the withdrawal of the hydrochloride of SevH. Treatment with SevH results in a significant increase in dietary acid load, and this is the main cause of the observed acidosis[4]. In favor of this is the observation that patients who switch from SevH to bixalomer, a non-hydrochloride and non-carbonate phosphate binder, improve their metabolic acidosis. This indicates that the withdrawal of chloride without the additional effect of carbonate is sufficient to ameliorate the acidosis[15]. Lastly, in our study, no correlation was found between LanC dose and acid-base parameters. The above support the hypothesis that the effect of the carbonate content of LanC on acid-base status is rather small. Moreover, concomitant use of CalC could compensate for the effects of loss of carbonate provided by the LanC on acid-base status. However, only two of our patients were on CalC, and the doses remained stable throughout the study. Finally, due to the small sample size of our study, a type II error cannot be excluded. Nevertheless, the harmful effect of SevH on acid-base balance was shown even in studies with 8 to 16 patients[7,15,16]. Thus, the effects of SFOH switching would probably be detected in our study if they were significant. In addition, finding a significant deference between the acid-base status of 2-d and 3-d interdialytic interval could be considered a supporting finding that despite the small sample size, differences were detected when they were significant.

In our study, SFOH was effective in controlling phosphate without increasing the pill burden, in accordance with previous studies[17,18]. However, some of our patients could not tolerate the new binder, as treatment with SFOH appears to be predominantly complicated by gastrointestinal disturbances[17,19].

Finally, we observed that patients were more acidotic in the long interdialytic interval. This has been already shown in previous studies[20], and this is why we decided to perform measurements both in the long and the short interdialytic interval in an effort to increase the possibility of detecting potential effects of SFOH switching on acid-base status.

The main limitation of the present study is the small sample size, as possible effects of switching on acid-base parameters may not be detected, even if present. Yet, the small number of patients allowed for stable conditions and better compliance, and this, together with the prospective nature, can be considered a strength of the study. Another limitation is that we did not measure the protein dietary intake that can affect acid-base balance. However, nutritional instructions remained the same during the study, and albumin and cholesterol levels did not change, supporting that there were no major changes in dietary habits. Finally, we cannot generalize our findings in patients with severe acidosis or in patients with ESKD on peritoneal dialysis.

To the best of our knowledge, this is the first study that evaluates acid-base status in patients receiving the

new phosphate binder SFOH. Therefore, it can serve as a pilot for further studies with a larger number of patients, different binders and extended durations to better understand their effect in clinically important outcomes, such as metabolic acidosis.

In conclusion, switching from LanC to SFOH did not have any significant effect on blood bicarbonate levels and gas analysis, indicating that there is no need to change hemodialysis prescription regarding these parameters. However, when selecting a phosphate binder, potential consequences on acid-base balance should be considered, and monitoring of serum bicarbonate levels is part of good clinical practice.

ARTICLE HIGHLIGHTS

Research background

The effect of phosphate binders in clinically important outcomes, such as metabolic acidosis, remains understudied.

Research motivation

There are no studies examining the effect of the novel phosphate binder sucroferric oxyhydroxide (SFOH) on acid-base status.

Research objectives

Examine possible alterations in acid-base parameters in hemodialysis patients switching from lanthanum carbonate (LanC) to SFOH.

Research methods

Fifteen stable hemodialysis patients switched from LanC to SFOH. We compared pre- and post-switching blood gas analyses, whilst hemodialysis conditions and medications remained stable.

Research results

Switching from LanC to the novel phosphate binder SFOH did not have any significant effect on blood bicarbonate levels and gas analysis. No correlations were found, either between pre-switching LanC daily dose or between post-switching daily dose of the new binder and the measured parameters.

Research conclusions

This is the first study that evaluates acid-base status in patients switching from LanC to the new phosphate binder SFOH, showing that there is no need to change hemodialysis prescription regarding these parameters.

Research perspectives

Our study can serve as a pilot for further studies with a larger number of patients, different binders and extended durations, to better understand their effect in clinically important outcomes, such as metabolic acidosis.

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