ISSN 2220-6124 (online)

World Journal of *Nephrology*

World J Nephrol 2018 October 10; 7(6): 117-128

Published by Baishideng Publishing Group Inc

World Journal of Nephrology

Contents

Volume 7 Number 6 October 10, 2018

ABOUT COVER

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World Journal of Nephrology (*WJN*) is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

NAME OF JOURNAL
World Journal of Nephrology

ISSN
ISSN 2220-6124 (online)

LAUNCH DATE
February 6, 2012

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All editorial board members resources online at http://www.wjgnet.com/2220-6124/editorialboard.htm

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PUBLICATION DATE
October 10, 2018

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World Journal of Nephrology

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World J Nephrol 2018 October 10; 7(6): 117-122

DOI: 10.5527/wjn.v7.i6.117

ISSN 2220-6124 (online)

MINIREVIEWS

Oral alkali therapy and the management of metabolic acidosis of chronic kidney disease: A narrative literature review

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Manuscript source: Unsolicited manuscript

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Received: May 7, 2018
Peer-review started: May 7, 2018
First decision: May 25, 2018
Revised: July 14, 2018
Accepted: August 30, 2018
Article in press: August 30, 2018
Published online: October 10, 2018

Abstract

Chronic metabolic acidosis is a common complication seen in advanced chronic kidney disease (CKD). There is currently no consensus on its management in the Republic of Ireland. Recent trials have suggested that appropriate active management of metabolic acidosis through oral alkali therapy and modified diet can have a deterring impact on CKD progression. The potential benefits of treatment include preservation of bone health and improvement in muscle function; however, present data is limited. This review highlights the current evidence, available primarily from randomised control trials (RCTs) over the last decade, in managing the metabolic acidosis of CKD and outlines ongoing RCTs that are promising. An economic perspective is also briefly discussed to support decision-making.

Key words: Chronic metabolic acidosis; Chronic kidney disease; Oral sodium bicarbonate; Oral alkali therapy; Health economics; Serum bicarbonate

Core tip: Chronic metabolic acidosis contributes to the progression of chronic kidney disease (CKD). We summarise and analyse current evidence regarding the management of the metabolic acidosis of CKD, as well as the potential benefits and adverse effects. We also offer novel therapeutic guidelines for clinicians, which include the most evidence-based range to maintain serum bicarbonate in the CKD patient population.

Ahmed AR, Lappin D. Oral alkali therapy and the management of metabolic acidosis of chronic kidney disease: A narrative literature review. *World J Nephrol* 2018; 7(6): 117-122 Available from: URL: http://www.wjgnet.com/2220-6124/full/v7/i6/117.htm DOI: http://dx.doi.org/10.5527/wjn.v7.i6.117

INTRODUCTION

The prevalence of chronic kidney disease (CKD) in the

Republic of Ireland is estimated to be around 4.5% in the general population, rising to around 11.6% in individuals over 45 years of age[1]. CKD management has a significant economic impact on the healthcare system, with the cost of care inversely proportional to a decline in renal function. Thus, interventions that can delay the progression of CKD will potentially contribute to an overall decrease in cost. This relation can be seen in economic evaluations of the RENAAL study, which demonstrated that early management of proteinuria in diabetic patients with losartan lead to a decrease in the progression to end-stage kidney disease and long-term health care costs. In fact, one of these studies was conducted in Canada, which has a public health care system relatively similar to Ireland[2-4].

There are relatively few modifiable factors in CKD management that can slow the progression of renal function decline. The management of hypertension, proteinuria and glycaemic control in patients with diabetes are the primary focuses with regards to delaying CKD progression[5,6]. In the last decade, however, a renewed interest in the treatment of metabolic acidosis of CKD (MA-CKD) has emerged and has been identified as an independent factor causing CKD progression[7-9].

MA-CKD is a complication commonly seen in patients with a glomerular filtration rate (GFR) less than 30 mL/min per 1.73 m^2 (CKD G4-5), and is defined as serum bicarbonate levels that are persistently less than 22 mmol/L[10,11]. It is associated with a worsening of CKD-mineral and bone disease, muscle wasting, hyperkalaemia, insulin resistance, hyperlipidaemia, and, most importantly, with the progression of CKD and increased mortality[7,12]. In Ireland, there is currently no consensus on the management of MA-CKD, such as when to initiate oral alkali therapy or introduce a less acidogenic diet. It is therefore important to assess and develop national guidelines on the complications like MA-CKD that can prove cost-effective for the health system and improve the long-term outcome of CKD patients[13].

MECHANISM OF INJURY

The most commonly proposed mechanism of injury associated with MA-CKD is related to renal ammonium metabolism. As CKD progresses, there is a loss of nephrons that is coupled with compensatory hypertrophy of the remaining nephrons to maintain acid balance. The hypertrophied nephrons increase their capacity to produce ammonia, which activates a complement pathway that leads to renal fibrosis and CKD progression[9]. Animal models and some observational studies have also demonstrated that a rise in endothelin levels and activation of the intrarenal renin-angiotensin system in response to acidosis may play a role in the pathogenesis of renal fibrosis[14-16].

ANALYSIS OF EVIDENCE

Animal models using alkali agents to treat metabolic acidosis have suggested a decline in CKD progression; however, the results were not consistent[17]. Numerous observational studies in human cohorts have demonstrated beneficial effects of oral alkali therapy on renal function[8,18,19]. The first randomised control trial (RCT) on this subject was published in 2009[7]. The trial involved a total of 134 patients with estimated glomerular filtration rate (eGFR) between 15-30 mL/min per 1.73 m^2 and serum bicarbonate between 16-20 mmol/L. Sixty-two patients were in the intervention group, which involved supplementation with sodium bicarbonate, with the aim of maintaining a serum bicarbonate level of more than 23 mmol/L. Sixty-seven patients were in the control group and did not receive any alkali supplementation over a two-year study period[7]. One of the primary outcomes shown was a significantly lower decline in creatinine clearance in the treatment group at 1.88 mL/min per 1.73 m^2 compared to 5.93 mL/min per 1.73 m^2 in the nontreated group.

Subsequently, an American RCT was published looking at this topic in 120 patients with hypertensive nephropathy who had eGFR between 60-90 mL/min per 1.73 m^2[20]. The patients were divided into three equal groups: A sodium bicarbonate intervention group, a sodium chloride group and a placebo group. All participants had normal baseline venous total carbon dioxide (equivalent to serum bicarbonate) averaging 26 mmol/L, and albuminuria of more than 300 mg/g[20]. Over five years of follow-up, there was a decrease in the rate of GFR decline of 1.47 mL/min per 1.73 m^2/year in the sodium bicarbonate group, compared to 2.05 mL/min per 1.73 m^2/year in the sodium chloride group and 2.13 mL/min per 1.73 m^2/year in the placebo group. The study demonstrated that even without overt metabolic acidosis, oral alkali therapy contributed significantly to slowing the progression of CKD.

Both of these studies were included in the NICE CKD guidelines, which were updated in 2014, and led the authors to recommend that medical teams should consider oral sodium bicarbonate supplementation in patients with GFR less than 30 mL/min per 1.73 m^2 and serum bicarbonate levels below 20 mmol/L, a recommendation not previously seen in NICE CKD guidelines[21,22]. The KDIGO 2012 CKD guidelines also suggested using oral bicarbonate therapy in the CKD patient population, but at a serum bicarbonate value of less than 22 mmol/L. This is a lesser biochemically overt acidosis used to initiate therapy, compared to the 2014 updated NICE CKD guidelines[23].

A shorter duration RCT (8-12 wk) consisting of 41 patients looked mainly at the effects of oral bicarbonate supplementation on thyroid function in the CKD population (GFR < 35 mL/min per 1.73 m^2) with serum bicarbonate levels less than 22 mmol/L[24]. The aim was to achieve serum bicarbonate > 24 mmol/L in the treatment group[24]. The results noted not only an improvement in thyroid function, but also a preservation of GFR in the treatment group compared to a decline

Table 1 Summary of evidence

RCT	Participants (*n*)	Intervention and aim	eGFR (mL/min per 1.73 m^2) baseline	Serum HCO_3 (mmol/L) at baseline	Duration (months)	Rate of Decline of eGFR (mL/min per 1.73 m^2)
De brito-ashurst *et al*[7]	Total: 134 Intervention: 62	Oral sodium bicarbonate tablets to maintain serum HCO_3 > 23 mmol/L	15-29	16-20	24	HCO_3 group: 1.88 Non treated group: 5.93
Mahajan *et al*[20]	Total: 120 Intervention: 30	Oral sodium bicarbonate tablets	60-89	26	60	HCO_3 group: 1.47 per year Non treated group: 2.05 per year
Goraya *et al*[26]	Total: 71 Intervention: 30	Oral sodium bicarbonate and F and V	15-29	< 22	12	HCO_3 and F and V groups: Preservation of eGFR
Goraya *et al*[27]	Total : 108 Intervention: 72	Oral sodium bicarbonate and F and V	30-59	22-24	36	Non treated group: 13.8 over 3 yr HCO_3: 5.4 over 3 yr F and V: 5.4 over 3 yr
Disthabanchong *et al*[24]	Total: 41 Intervention: 21	Oral sodium bicarbonate to maintain serum bicarbonate > 24 mmol/L	< 35	< 22	2-3	HCO_3 group: Preservation of eGFR Non treated group: 1.3

RCT: Randomised control trials; eGFR: Estimated glomerular filtration rate; F and V: Fruits and Vegetables

in GFR of 1.3 mL/min per 1.73 m^2 in the control group over the time period studied.

In 2012, a systematic review with a meta-analysis consisting of six RCTs on oral alkali therapy and its effects on renal function found a net improvement in GFR of 3.2 mL/min per 1.73 m^2 (based on 248 patients) compared to the non bicarbonate therapy group. The authors of this study suggested recommendations similar to the KDIGO 2012 CKD guidelines[25].

Goraya *et al*[26] compared a fruit and vegetable diet with oral bicarbonate supplementation in 71 CKD G4 hypertensive nephropathy patients with serum bicarbonate levels less than 22 mmol/L who were followed for one year. Markers of kidney injury, as proposed by the research team, included 8 h urine excretion of N-acetyl β-d-glucosaminidase, albumin and TGF-β, all of which were lower at the one-year follow-up compared to baseline. Notably, GFR was preserved in both groups. Both groups demonstrated an improvement in serum bicarbonate levels, but more was seen with oral alkali supplementation (21.2 ± 1.3 mmol/L *vs* 19.5 ± 1.59 mmol/L baseline and 19.3 ± 1.9 mmol/L baseline *vs* 19.9 ± 1.7 mmol/L). Interestingly, plasma potassium did not change significantly in the fruit and vegetable group (all patients were on furosemide, and patients with serum potassium more than 4.6 mmol/L were excluded).

Goraya *et al*[27] performed another RCT over a three-year period looking at CKD G3 hypertensive nephropathy patients with serum bicarbonate levels (total venous CO_2) between 22-24 mmol/L. These patients were divided into three groups of 36: An oral bicarbonate supplementation group, fruit and vegetable group and standard treatment group. All three groups received an angiotensin-converting enzyme (ACE) inhibitor with the goal to maintain a target systolic blood pressure of less than 130 mmHg. The outcome was a greater reduction in urinary albumin in both the bicarbonate and fruit and vegetable group compared to the standard care group, a reduction in N-acetyl β-d-glucosaminidase and urinary angiotensinogen in the bicarbonate and fruit and vegetable groups compared to a rise in the standard care group, and slower progression of GFR decline in the bicarbonate and fruit and vegetable group compared to the standard care group.

There are a few RCTs currently ongoing or actively recruiting, which may further shed light on the effectiveness of oral alkali therapy in preserving renal function, as well as other potential benefits such as an improvement in muscle strength and cardiac function[28-32]. The Bicarb Trial is perhaps the most comprehensive of the current ongoing RCTs, involving multiple United Kingdom centers with 380 CKD G4-5 participants aged 60 or older and with serum bicarbonate levels < 22 mmol/L[29]. The trial will look at the efficacy of oral sodum bicarbonate supplementation on physical performance, renal function, blood pressure, proteinuria and cost-effectiveness. Another ongoing RCT looking at renal transplant recipients with serum bicarbonate levels < 22 mmol/L and GFR between 15-89 mL/min per 1.73 m^2 could potentially enhance our understanding of the benefits of treating metabolic acidosis on transplant physiology[32]. It will also cover a cohort of patients (renal transplant recipients) that have not formally been studied regarding chronic metabolic acidosis. The results of these RCTs are highly anticipated (Table 1).

OTHER POTENTIAL BENEFITS

CKD patients have a higher risk of fractures compared to the general population, largely due to a decrease in 1,25 hydroxylation of calcidiol (25-OH-vitamin D) and secondary hyperparathyroidism. Bone is also used as a buffer for excess hydrogen ions in chronic metabolic acidosis, which leads to a loss of calcium and an exacerbation of bone fragility[33].

The preservation of bone health and the stabilisation of parathyroid hormone by the correction of metabolic acidosis has been demonstrated in a few studies[34-36]. Furthermore, a decrease in protein degradation is seen, at a biochemical level, with an increase in muscle mass and an improvement in physical function[7,37-39].

POTENTIAL ADVERSE EFFECTS

There has always been a concern regarding the worsening of hypertension, fluid overload and congestive heart failure (CHF) after the administration of oral sodium-based alkali supplementation in the CKD population due to sodium loading. These potential theoretical adverse effects have not been proven in a clinical setting, although a majority of participants in the RCTs were excluded if uncontrolled hypertension or clinically overt CHF was present[7,25]. In one RCT, blood pressure was noted to be similar between the bicarbonate and standard care groups, with no CHF-related hospitalisation, and a similar increase in the use of diuretics and antihypertensive agents over the course of the study[7]. Goraya *et al*[27] reported a similar finding, with no significant difference in blood pressure between the standard care and bicarbonate-treated groups, and a similar requirement for enalapril. Two RCTs by Goraya *et al*[26,27] also demonstrated that a fruit and vegetable diet allowed better blood pressure control compared to both bicarbonate supplementation and standard care.

TRC 101, a novel sodium-free, non-absorbed hydrochloric acid binder, has shown efficacy in alleviating MA-CKD without effecting blood pressure, and may become widely available in the near future[40].

A plausible risk of increased vascular calcification exists once an acidotic environment has been resolved with oral alkali supplementation. However, there is currently a scarcity of studies to conclusively demonstrate this phenomenon[41].

RECOMMENDATIONS

An appraisal of current evidence is necessary for the appropriate management of MA-CKD, which could have a significant impact on CKD care in Ireland.

A few RCTs demonstrated that a fruit and vegetable diet reduced the overall acid load and had a renoprotective effect[26,27]. Two interesting observations can be noted. Firstly, the RCT with serum bicarbonate levels < 22 mmol/L in the CKD G4 hypertensive nephropathy population did not achieve the desired aim of serum bicarbonate levels of > 22 mmol/L with fruits and vegetables. Despite this, however, the urinary indices of renal injury were lower and GFR was preserved[26]. Secondly, the RCT on the CKD G3 hypertensive nephropathy population with serum bicarbonate levels between 22-24 mmol/L, above the current treatment guidelines, also demonstrated a slower progression of GFR decline and a reduction in urinary indices of renal injury with oral alkali supplementation[26,27]. Even when oral alkali therapy was used in patients with CKD G2 and normal serum bicarbonate levels, a decline in the reduction of GFR was observed[20]. These findings correlate with the understanding that western, high animal meat diets are indirectly renotoxic due to their overall acid-inducing effect, and that alkaline agents, either fruits and vegetables or oral sodium bicarbonate, help to neutralize this excess acid[42,43].

It can be postulated that when fruits and vegetables associated with an alkaline effect are incorporated into a diet, they will be renoprotective at any CKD stage because of their ability to buffer acid. However, CKD G4-G5 patients have a tendency towards hyperkalemia. The RCT involving CKD G4-G5 patients managed with fruits and vegetables were on furosemide. Thus, the use of high potassium-containing fruits and vegetables in this category remains controversial[26].

Based on the current evidence, it can be suggested that the CKD population maintain a serum bicarbonate level above 22 mmol/L, and that oral alkali therapy should be utilised to achieve this, especially in CKD G4-G5 patients[7,20,24-27]. Since none of the RCTs included uncontrolled hypertension and overt CHF patients, clinical judgment should be used when initiating oral alkali therapy in patients with an underlying history of CHF or hypertension requiring more than three agents to control[7,20,26,27,37].

The upper limit of serum bicarbonate levels once on oral alkali therapy is still speculative, with limited data available. In one cohort study, a serum bicarbonate level of > 26 mmol/L was associated with increased mortality and a risk of heart failure, while another study on haemodialysis patients demonstrated an association with increased mortality when serum bicarbonate levels were > 27 mmol/L[44,45].

Maintaining serum bicarbonate levels between 22-26 mmol/L in the CKD population would be closest to the evidence base available at the moment. In four of the RCTs, an average of 0.3 mEq/kg per day to 1 mEq/kg per day of oral sodium bicarbonate was used to achieve the desired aim of serum bicarbonate levels > 22 mmol/L[7,20,26,27,37].

It is further suggested that dieticians in renal units get involved in designing a program for CKD G1-G3 regardless of serum bicarbonate that incorporates fruits and vegetables to reduce the overall acid load, and commence community programs to promote this.

DOSING AND COST

A 1 mg dose of sodium bicarbonate approximately equates to 0.0123 mEq. A 600 mg sodium bicarbonate tablet contains 7.4 mEq of bicarbonate, and the usual commencing dose is 600 mg three times daily. In a 70 kg patient, this is approximately 0.3 mEq/kg per day. Three additional tablets may have patient compliance issues, as sodium bicarbonate can lead to abdominal bloating. However, until preparation is optimized and other formulations including sodium citrate are commonly available, oral sodium bicarbonate tablets will need to be titrated as required to achieve the desired serum bicarbonate levels between 22-26 mmol/L. An unconventional approach is to utilise natural baking soda (sodium bicarbonate), of which one teaspoon is equal to approximately 5000 mg of sodium bicarbonate. Thus, one-half of a teaspoon mixed in water should produce 2500 mg, which is equivalent to 31 mEq (2500 x 0.0123) of sodium bicarbonate. The cost per 600 mg of sodium bicarbonate tablets (including enteric-coated tablets) is approximately 0.1-0.15 Euros. If used at 0.3 mEq/Kg per day, it would cost 109-170 Euros/year (for a 70 kg patient).

CONCLUSION

MA-CKD is a complication that is often overlooked in clinical practice. Current evidence suggests that it contributes to renal function decline, and that appropriate management would lead to better CKD outcomes in terms of renal function preservation, muscle function, bone health and economic burden. Oral alkali therapy has the potential, when combined with other known interventions like blood pressure control and glycaemic control, to prolong the time before reaching end-stage renal disease. Irish nephrology practices currently hold very diverse opinions on managing MA-CKD. The recommendations offered here can be used as a basis to develop more detailed guidelines in the Republic of Ireland and around the world. Larger ongoing RCTs highlighted in this review will perhaps provide more conclusive evidence.

REFERENCES

1 **Stack AG**, Casserly LF, Cronin CJ, Chernenko T, Cullen W, Hannigan A, Saran R, Johnson H, Browne G, Ferguson JP. Prevalence and variation of Chronic Kidney Disease in the Irish health system: initial findings from the National Kidney Disease Surveillance Programme. *BMC Nephrol* 2014; **15**: 185 [PMID: 25425510 DOI: 10.1186/1471-2369-15-185]

2 **Palmer AJ**, Valentine WJ, Chen R, Mehin N, Gabriel S, Bregman B, Rodby RA. A health economic analysis of screening and optimal treatment of nephropathy in patients with type 2 diabetes and hypertension in the USA. *Nephrol Dial Transplant* 2008; **23**: 1216-1223 [PMID: 18359872 DOI: 10.1093/ndt/gfn082]

3 **Burgess ED**, Carides GW, Gerth WC, Marentette MA, Chabot I; Canadian Hypertension Society. Losartan reduces the costs associated with nephropathy and end-stage renal disease from type 2 diabetes: Economic evaluation of the RENAAL study from a Canadian perspective. *Can J Cardiol* 2004; **20**: 613-618 [PMID: 15152291]

4 **Herman WH**, Shahinfar S, Carides GW, Dasbach EJ, Gerth WC, Alexander CM, Cook JR, Keane WF, Brenner BM. Losartan reduces the costs associated with diabetic end-stage renal disease: the RENAAL study economic evaluation. *Diabetes Care* 2003; **26**: 683-687 [PMID: 12610022 DOI: 10.2337/diacare.26.3.683]

5 **Upadhyay A**, Uhlig K. Is the lower blood pressure target for patients with chronic kidney disease supported by evidence? *Curr Opin Cardiol* 2012; **27**: 370-373 [PMID: 22525328 DOI: 10.1097/HCO.0b013e328353b934]

6 **Levey AS**, Coresh J. Chronic kidney disease. *Lancet* 2012; **379**: 165-180 [PMID: 21840587 DOI: 10.1016/S0140-6736(11)60178-5]

7 **de Brito-Ashurst I**, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009; **20**: 2075-2084 [PMID: 19608703 DOI: 10.1681/ASN.2008111205]

8 **Shah SN**, Abramowitz M, Hostetter TH, Melamed ML. Serum bicarbonate levels and the progression of kidney disease: a cohort study. *Am J Kidney Dis* 2009; **54**: 270-277 [PMID: 19394734 DOI: 10.1053/j.ajkd.2009.02.014]

9 **Nath KA**, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. *J Clin Invest* 1985; **76**: 667-675 [PMID: 2993363 DOI: 10.1172/JCI112020]

10 **Moranne O**, Froissart M, Rossert J, Gauci C, Boffa JJ, Haymann JP, M'rad MB, Jacquot C, Houillier P, Stengel B, Fouqueray B; NephroTest Study Group. Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol* 2009; **20**: 164-171 [PMID: 19005010 DOI: 10.1681/ASN.2008020159]

11 **Kraut JA**, Madias NE. Metabolic Acidosis of CKD: An Update. *Am J Kidney Dis* 2016; **67**: 307-317 [PMID: 26477665 DOI: 10.1053/j.ajkd.2015.08.028]

12 **Chen W**, Abramowitz MK. Treatment of metabolic acidosis in patients with CKD. *Am J Kidney Dis* 2014; **63**: 311-317 [PMID: 23932089 DOI: 10.1053/j.ajkd.2013.06.017]

13 **Jha V**, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; **382**: 260-272 [PMID: 23727169 DOI: 10.1016/S0140-6736(13)60687-X]

14 **Wesson DE**, Nathan T, Rose T, Simoni J, Tran RM. Dietary protein induces endothelin-mediated kidney injury through enhanced intrinsic acid production. *Kidney Int* 2007; **71**: 210-217 [PMID: 17164833 DOI: 10.1038/sj.ki.5002036]

15 **Ng HY**, Chen HC, Tsai YC, Yang YK, Lee CT. Activation of intrarenal renin-angiotensin system during metabolic acidosis. *Am J Nephrol* 2011; **34**: 55-63 [PMID: 21659740 DOI: 10.1159/000328742]

16 **Wesson DE**, Simoni J, Broglio K, Sheather S. Acid retention accompanies reduced GFR in humans and increases plasma levels of endothelin and aldosterone. *Am J Physiol Renal Physiol* 2011; **300**: F830-F837 [PMID: 21270096 DOI: 10.1152/ajprenal.00587.2010]

17 **Gadola L**, Noboa O, Márquez MN, Rodriguez MJ, Nin N, Boggia J, Ferreiro A, García S, Ortega V, Musto ML, Ponte P, Sesser P, Pizarrosa C, Ravaglio S, Vallega A. Calcium citrate ameliorates the progression of chronic renal injury. *Kidney Int* 2004; **65**: 1224-1230 [PMID: 15086461 DOI: 10.1111/j.1523-1755.2004.00496.x]

18 **Raphael KL**, Wei G, Baird BC, Greene T, Beddhu S. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. *Kidney Int* 2011; **79**: 356-362 [PMID: 20962743 DOI: 10.1038/ki.2010.388]

19 **Kovesdy CP**, Kalantar-Zadeh K. Oral bicarbonate: renoprotective in CKD? *Nat Rev Nephrol* 2010; **6**: 15-17 [PMID: 20023686 DOI: 10.1038/nrneph.2009.204]

20 **Mahajan A**, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int* 2010; **78**: 303-309 [PMID: 20445497

DOI: 10.1038/ki.2010.129]
21 **National Clinical Guideline Centre (UK)**. Chronic Kidney Disease (Partial Update): Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care, 2014 [PMID: 25340245]
22 **Crowe E**, Halpin D, Stevens P; Guideline Development Group. Early identification and management of chronic kidney disease: summary of NICE guidance. *BMJ* 2008; **337**: a1530 [PMID: 18824486 DOI: 10.1136/bmj.a1530]
23 **Levin A**, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney Int* 2014; **85**: 49-61 [PMID: 24284513 DOI: 10.1038/ki.2013.444]
24 **Disthabanchong S**, Treeruttanawanich A. Oral sodium bicarbonate improves thyroid function in predialysis chronic kidney disease. *Am J Nephrol* 2010; **32**: 549-556 [PMID: 21042013 DOI: 10.1159/000321461]
25 **Susantitaphong P**, Sewaralthahab K, Balk EM, Jaber BL, Madias NE. Short- and long-term effects of alkali therapy in chronic kidney disease: a systematic review. *Am J Nephrol* 2012; **35**: 540-547 [PMID: 22653322 DOI: 10.1159/000339329]
26 **Goraya N**, Simoni J, Jo CH, Wesson DE. A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. *Clin J Am Soc Nephrol* 2013; **8**: 371-381 [PMID: 23393104 DOI: 10.2215/CJN.02430312]
27 **Goraya N**, Simoni J, Jo CH, Wesson DE. Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. *Kidney Int* 2014; **86**: 1031-1038 [PMID: 24694986 DOI: 10.1038/ki.2014.83]
28 **Alkali therapy in chronic Kidney Disease**. [accessed 2011 Oct 14]. In: ClinicalTrials.gov [Internet]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT01452412 ClinicalTrials.gov Identifier: NCT01452412
29 **Witham MD**, Band MM, Littleford RC, Avenell A, Soiza RL, McMurdo ME, Sumukadas D, Ogston SA, Lamb EJ, Hampson G, McNamee P; BiCARB Study Group. Does oral sodium bicarbonate therapy improve function and quality of life in older patients with chronic kidney disease and low-grade acidosis (the BiCARB trial)? Study protocol for a randomized controlled trial. *Trials* 2015; **16**: 326 [PMID: 26231610 DOI: 10.1186/s13063-015-0843-6]
30 **Bicarbonate Administration in CKD**. [accessed 2016 Sep 27]. In: ClinicalTrials.gov [Internet]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02915601 ClinicalTrials.gov Identifier: NCT02915601
31 **Efficacy, Safety Study and Benefit of Alkali Therapy in Sickle Cell Disease**. [accessed 2013 Jul 10]. In: ClinicalTrials.gov [Internet]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT01894594 ClinicalTrials.gov Identifier: NCT01894594
32 **Preserve-Transplant Study**. [accessed 2017 Apr 6]. In: ClinicalTrials.gov [Internet]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT03102996 ClinicalTrials.gov Identifier: NCT03102996
33 **Alpern RJ**, Sakhaee K. The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. *Am J Kidney Dis* 1997; **29**: 291-302 [PMID: 9016905 DOI: 10.1016/S0272-6386(97)90045-7]
34 **Mathur RP**, Dash SC, Gupta N, Prakash S, Saxena S, Bhowmik D. Effects of correction of metabolic acidosis on blood urea and bone metabolism in patients with mild to moderate chronic kidney disease: a prospective randomized single blind controlled trial. *Ren Fail* 2006; **28**: 1-5 [PMID: 16526312 DOI: 10.1080/08860220500461187]
35 **McSherry E**, Morris RC Jr. Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. *J Clin Invest* 1978; **61**: 509-527 [PMID: 621287 DOI: 10.1172/JCI108962]
36 **Sebastian A**, Morris RC Jr. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994; **331**: 279 [PMID: 8015587 DOI: 10.1056/NEJM199407283310421]
37 **Abramowitz MK**, Melamed ML, Bauer C, Raff AC, Hostetter TH. Effects of oral sodium bicarbonate in patients with CKD. *Clin J Am Soc Nephrol* 2013; **8**: 714-720 [PMID: 23393105 DOI: 10.2215/CJN.08340812]
38 **Graham KA**, Reaich D, Channon SM, Downie S, Gilmour E, Passlick-Deetjen J, Goodship TH. Correction of acidosis in CAPD decreases whole body protein degradation. *Kidney Int* 1996; **49**: 1396-1400 [PMID: 8731105]
39 **Reaich D**, Channon SM, Scrimgeour CM, Daley SE, Wilkinson R, Goodship TH. Correction of acidosis in humans with CRF decreases protein degradation and amino acid oxidation. *Am J Physiol* 1993; **265**: E230-E235 [PMID: 8396331 DOI: 10.1152/ajpendo.1993.265.2.E230]
40 **Bushinsky DA**, Hostetter T, Klaerner G, Stasiv Y, Lockey C, McNulty S, Lee A, Parsell D, Mathur V, Li E, Buysse J, Alpern R. Randomized, Controlled Trial of TRC101 to Increase Serum Bicarbonate in Patients with CKD. *Clin J Am Soc Nephrol* 2018; **13**: 26-35 [PMID: 29102959 DOI: 10.2215/CJN.07300717]
41 **de Solis AJ**, González-Pacheco FR, Deudero JJ, Neria F, Albalate M, Petkov V, Susanibar L, Fernandez-Sanchez R, Calabia O, Ortiz A, Caramelo C. Alkalinization potentiates vascular calcium deposition in an uremic milieu. *J Nephrol* 2009; **22**: 647-653 [PMID: 19809998]
42 **Adeva MM**, Souto G. Diet-induced metabolic acidosis. *Clin Nutr* 2011; **30**: 416-421 [PMID: 21481501 DOI: 10.1016/j.clnu.2011.03.008]
43 **Della Guardia L**, Roggi C, Cena H. Diet-induced acidosis and alkali supplementation. *Int J Food Sci Nutr* 2016; **67**: 754-761 [PMID: 27338594 DOI: 10.1080/09637486.2016.1198889]
44 **Dobre M**, Yang W, Pan Q, Appel L, Bellovich K, Chen J, Feldman H, Fischer MJ, Ham LL, Hostetter T, Jaar BG, Kallem RR, Rosas SE, Scialla JJ, Wolf M, Rahman M; CRIC Study Investigators. Persistent high serum bicarbonate and the risk of heart failure in patients with chronic kidney disease (CKD): A report from the Chronic Renal Insufficiency Cohort (CRIC) study. *J Am Heart Assoc* 2015; **4**: pii: e001599 [PMID: 25896890 DOI: 10.1161/JAHA.114.001599]
45 **Wu DY**, Shinaberger CS, Regidor DL, McAllister CJ, Kopple JD, Kalantar-Zadeh K. Association between serum bicarbonate and death in hemodialysis patients: is it better to be acidotic or alkalotic? *Clin J Am Soc Nephrol* 2006; **1**: 70-78 [PMID: 17699193 DOI: 10.2215/CJN.0001050]

P- Reviewer: Keramati MR, Raikou VD, Sakhaee K, Stolic RV
S- Editor: Cui LJ **L- Editor**: Filipodia **E- Editor**: Huang Y

World Journal of Nephrology

Submit a Manuscript: http://www.f6publishing.com

World J Nephrol 2018 October 10; 7(6): 123-128

DOI: 10.5527/wjn.v7.i6.123

ISSN 2220-6124 (online)

ORIGINAL ARTICLE

Observational Study

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

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Author contributions: All of the authors contributed to the study design; Stavroulopoulos A, Aresti V and Papadopoulos C collected the data; Stavroulopoulos A analyzed the data and drafted the manuscript; all authors contributed to the conception of the paper, interpretation of data, and subsequent revisions of the manuscript.

Institutional review board statement: The protocol for the research project has been approved by the IASIO Hospital's Ethics Committee and conforms to the provisions of the Declaration of Helsinki.

Informed consent statement: Informed written consent was obtained from all patients before they entered the study.

Conflict-of-interest statement: None to declare.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Manuscript source: Invited manuscript

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Received: June 4, 2018
Peer-review started: June 4, 2018
First decision: July 11, 2018
Revised: August 2, 2018
Accepted: August 30, 2018
Article in press: August 30, 2018
Published online: October 10, 2018

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.

Stavroulopoulos A, Aresti V, Papadopoulos C, Nennes P, Metaxaki P, Galinas A. Bicarbonate levels in hemodialysis patients switching from lanthanum carbonate to sucroferric oxyhydroxide. *World J Nephrol* 2018; 7(6): 123-128 Available from: URL: http://www.wjgnet.com/2220-6124/full/v7/i6/123.htm DOI: http://dx.doi.org/10.5527/wjn.v7.i6.123

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.

REFERENCES

1 **Kraut JA**, Madias NE. Metabolic Acidosis of CKD: An Update. *Am J Kidney Dis* 2016; **67**: 307-317 [PMID: 26477665 DOI: 10.1053/j.ajkd.2015.08.028]

2 **Bommer J**, Locatelli F, Satayathum S, Keen ML, Goodkin DA, Saito A, Akiba T, Port FK, Young EW. Association of predialysis serum bicarbonate levels with risk of mortality and hospitalization in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2004; **44**: 661-671 [PMID: 15384017]

3 **Thet Z**, Win AK, Pedagogos E, Beavis J, Crikis S, Nelson C. Differential effects of phosphate binders on pre-dialysis serum bicarbonate in end-stage kidney disease patients on maintenance haemodialysis. *BMC Nephrol* 2013; **14**: 205 [PMID: 24079654 DOI: 10.1186/1471-2369-14-205]

4 **Brezina B**, Qunibi WY, Nolan CR. Acid loading during treatment with sevelamer hydrochloride: mechanisms and clinical implications. *Kidney Int Suppl* 2004; S39-S45 [PMID: 15296506 DOI: 10.1111/j.1523-1755.2004.09007.x]

5 **Oka Y**, Miyazaki M, Matsuda H, Takatsu S, Katsube R, Mori T, Takehara K, Umeda Y, Uno F. Sevelamer hydrochloride dose-dependent increase in prevalence of severe acidosis in hemodialysis patients: analysis of nationwide statistical survey in Japan. *Ther Apher Dial* 2014; **18**: 37-43 [PMID: 24499082 DOI: 10.1111/1744-9987.12052]

6 **Matsushita Y**, Yamnouchi E, Matsuoka K, Arizono K. Effect of calcium carbonate administration on metabolic acidosis induced by sevelamer hydrochloride in chronic hemodialysis patients. *J Jpn Soc Dial Ther* 2006; **39**: 1245-1250 [DOI: 10.4009/jsdt.39.1245]

7 **Filiopoulos V**, Koutis I, Trompouki S, Hadjiyannakos D, Lazarou D, Vlassopoulos D. Lanthanum carbonate versus sevelamer hydrochloride: improvement of metabolic acidosis and hyperkalemia in hemodialysis patients. *Ther Apher Dial* 2011; **15**: 20-27 [PMID: 21272248 DOI: 10.1111/j.1744-9987.2010.00868.x]

8 **Pai AB**, Shepler BM. Comparison of sevelamer hydrochloride and sevelamer carbonate: risk of metabolic acidosis and clinical implications. *Pharmacotherapy* 2009; **29**: 554-561 [PMID: 19397463 DOI: 10.1592/phco.29.5.554]

9 **Fan S**, Ross C, Mitra S, Kalra P, Heaton J, Hunter J, Plone M, Pritchard N. A randomized, crossover design study of sevelamer carbonate powder and sevelamer hydrochloride tablets in chronic kidney disease patients on haemodialysis. *Nephrol Dial Transplant* 2009; **24**: 3794-3799 [PMID: 19666658 DOI: 10.1093/ndt/gfp372]

10 **Habbous S**, Przech S, Acedillo R, Sarma S, Garg AX, Martin J. The efficacy and safety of sevelamer and lanthanum versus calcium-containing and iron-based binders in treating hyperphosphatemia in patients with chronic kidney disease: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2017; **32**: 111-125 [PMID: 27651467 DOI: 10.1093/ndt/gfw312]

11 **Cozzolino M**, Funk F, Rakov V, Phan O, Teitelbaum I. Preclinical Pharmacokinetics, Pharmacodynamics and Safety of Sucroferric Oxyhydroxide. *Curr Drug Metab* 2014; **15**: 953-965 [PMID: 25658128]

12 **Cernaro V**, Santoro D, Lacquaniti A, Costantino G, Visconti L, Buemi A, Buemi M. Phosphate binders for the treatment of chronic kidney disease: role of iron oxyhydroxide. *Int J Nephrol Renovasc Dis* 2016; **9**: 11-19 [PMID: 26893577 DOI: 10.2147/IJNRD.S78040]

13 **Velphoro Drug Approval Package FDA**. [Accessed 13 Nov 2017]. Available from: URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205109Orig1s000ChemR.pdf

14 **Block GA**, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, Allison MA, Asplin J, Smits G, Hoofnagle AN, Kooienga L, Thadhani R, Mannstadt M, Wolf M, Chertow GM. Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol* 2012; **23**: 1407-1415 [PMID: 22822075 DOI: 10.1681/ASN.2012030223]

15 **Sanai T**, Tada H, Ono T, Fukumitsu T. Phosphate binders and metabolic acidosis in patients undergoing maintenance hemodialysis—sevelamer hydrochloride, calcium carbonate, and bixalomer. *Hemodial Int* 2015; **19**: 54-59 [PMID: 24980286 DOI: 10.1111/hdi.12188]

16 **Gallieni M**, Cozzolino M, Brancaccio D. Transient decrease of serum bicarbonate levels with Sevelamer hydrochloride as the phosphate binder. *Kidney Int* 2000; **57**: 1776-1777 [PMID: 10809607 DOI: 10.1046/j.1523-1755.2000.00025.x]

17 **Floege J**, Covic AC, Ketteler M, Rastogi A, Chong EM, Gaillard S, Lisk LJ, Sprague SM; PA21 Study Group. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. *Kidney Int* 2014; **86**: 638-647 [PMID: 24646861 DOI: 10.1038/ki.2014.58]

18 **Coyne DW**, Ficociello LH, Parameswaran V, Anderson L, Vemula S, Ofsthun NJ, Mullon C, Maddux FW, Kossmann RJ, Sprague SM. Real-world effectiveness of sucroferric oxyhydroxide in

patients on chronic hemodialysis: A retrospective analysis of pharmacy data. *Clin Nephrol* 2017; **88**: 59-67 [PMID: 28587714 DOI: 10.5414/CN109021]

19 **Wüthrich RP**, Chonchol M, Covic A, Gaillard S, Chong E, Tumlin JA. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. *Clin J Am Soc Nephrol* 2013; **8**: 280-289 [PMID: 23124782 DOI: 10.2215/CJN.08230811]

20 **Graham KA**, Hoenich NA, Goodship TH. Pre and interdialytic acid-base balance in hemodialysis patients. *Int J Artif Organs* 2001; **24**: 192-196 [PMID: 11394698]

P- Reviewer: Choi MR, Ekpenyong CEE, Kilinc M, Nechifor G, Tiwari S
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