

Effect of switching from sevelamer hydrochloride to lanthanum carbonate on metabolic acidosis in dialysis patients

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Treatments for hyperphosphatemia in dialysis patients include dietary therapy and oral administration of phosphate binders; however, it has recently been suggested that oral administration of sevelamer hydrochloride, a phosphate binder, may cause metabolic acidosis. Owing to the decreased supply of sevelamer hydrochloride after the Eastern Japan Great Earthquake Disaster on March 11, 2011, hyperphosphatemia patients switched to another phosphate binder, lanthanum carbonate. Here, we retrospectively evaluated the effect of this medication substitution on metabolic acidosis in patients on maintenance hemodialysis. 32 patients, who underwent maintenance hemodialysis at Nagasaki Kidney Center in Japan, were enrolled in our study and followed to evaluate the effect of switching medication on metabolic acidosis at 3 months after switching from sevelamer hydrochloride to lanthanum carbonate. The mean dose of sevelamer hydrochloride prior to the earthquake disaster was 3 g/day, and the mean dose of lanthanum carbonate thereafter was 0.9 g/day. Three months after the medication was changed, the concentration of bicarbonate ion did not increase significantly ($p = 0.186$), whereas pH and base excess increased significantly ($p = 0.007$ and $p = 0.036$, respectively). In this study, although the HCO_3^- level was not significantly changed, the pH and base excess were significantly increased. Our findings indicate that lanthanum carbonate ameliorates metabolic acidosis.

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Introduction

In patients with chronic kidney disease, as renal function declines, hyperphosphatemia progresses with low urinary excretion of phosphate. Hyperphosphatemia is considered to be an important factor in the progression of vascular calcification in end-stage renal disease⁽¹⁾. It has also been shown that in dialysis patients, hyperphosphatemia is not only strongly associated with cardiovascular complications

due to vascular calcification and progress in secondary hyperparathyroidism, but also lowers life expectancy⁽²⁾. Target levels of pre-dialysis phosphorus (P) in blood are set at 3.5–6.0 mg/dL in dialysis patients in Japan, according to the Japanese guidelines⁽³⁾. In most of dialysis patients, control of blood P levels requires dietary restriction and oral administration of appropriate phosphate binders. Currently, there are 2 types of phosphate binders: calcium (Ca)-containing and non-Ca containing binders. However, the Ca

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load is also a promoting factor for vascular calcification^(4,5). Thus, in the 2003 K/DOQI “Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease,” published in the U.S., the upper limit for the Ca dosage from Ca-containing phosphate binders is set at 1500 mg/day. Consequently, for patients in whom control of blood P levels is challenging, it is recommended the use of phosphate binders that do not contain Ca.

Sevelamer hydrochloride (SH), a phosphate binder, which does not contain Ca, has been used in Japan since 2003. Studies comparing the effects of SH and Ca-containing phosphate binders on vascular calcification in dialysis patients showed that vascular calcification was markedly suppressed in the SH group^(4,5). Additionally, SH was shown to lower cholesterol levels⁽⁵⁾. However, it is well known that SH may cause gastrointestinal side effects, such as abdominal distention and constipation, and some studies reported that SH may exacerbate metabolic acidosis in a dose-dependent manner⁽⁶⁾; thus, SH should be used carefully.

Meanwhile, lanthanum is a rare earth with a very high affinity for phosphate—it reacts with phosphate to form a hardly-soluble salt. Lanthanum carbonate (LaC) is made by exploiting this high affinity between the lanthanum ion and phosphate, and is used to decrease the absorption of phosphate from food in dialysis patients. In Japan, LaC has also been used as a non-Ca-containing phosphate binder since 2009. It is considered that LaC does not have harmful effects on metabolic acidosis, because it does not contain hydrochloric acid; however, this has not yet been clearly demonstrated. Furthermore, there are very limited data regarding the long-term effects of LaC on the human body, including its accumulation and toxicity, and further follow-up studies are needed.

Thus, SH and LaC have different effects on metabolic acidosis, despite of the drugs used as phosphate binders. Currently, it has been suggested that a decreased level of pre-dialysis bicarbonate (HCO_3^-), a marker of acidosis/acid–base balance, may have harmful effects on bone metabolism and protein/amino acid metabolism, increase the frequency of hospital admission, and lower life expectancy in hemodialysis patients⁽⁷⁾. However, there are only a few studies to investigate the effects on metabolic acidosis by a switching of phosphate binder until now.

On March, 2011, a part of the plant and equipment of the manufacturer of SH in Japan were damaged by the Tohoku-Pacific Ocean Earthquake (Eastern Japan Great Earthquake Disaster). Therefore, the supply of SH declined, and patients who had been using SH were required to switch from SH to LaC. Thus, in this study, we retrospectively evaluated the

effects of LaC on metabolic acidosis in Japanese hemodialysis patients living in Nagasaki previously on SH due to the Eastern Japan Great Earthquake Disaster.

Patients and methods

Patients

Ethical approval was obtained from the Special Committee of Nagasaki University Hospital (project registration number 12052811) before commencement of the study.

This study included 32 outpatients on hemodialysis in the Nagasaki Kidney Center, who had been using oral SH (Renagel[®], Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) for treatment of hyperphosphatemia and who had switched to LaC (Fosrenol[®], Bayer AG, Leverkusen, Germany) after the Great East Japan Earthquake Disaster.

Study design

We collected the patient characteristics, laboratory data, medication, and adverse events from the patients' medical records. We used laboratory data measured immediately before the next hemodialysis session, after the maximum interval. The Ca levels were corrected based on the serum albumin level. The parathyroid hormone level (PTH) was measured as intact PTH by CLEIA (BML, INC., Tokyo, Japan). Thereafter, we retrospectively compared the results of laboratory investigations before and at least 3 months after the switch from SH to LaC. Patients already taking CaCO_3 , cinacalcet hydrochloride (Regpara[®], Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan) or vitamin D formulations for treatment of mineral and bone disorders associated with chronic kidney disease, in addition to phosphate binders, continued to take these agents after switching to LaC. Selection and dosages of these concomitant medications were in accordance with the “Guidelines for the management of secondary hyperparathyroidism in chronic dialysis patients,” published by the Japanese Society for Dialysis Therapy in 2006, and medication dosages were adjusted to achieve target levels of P (3.5–6 mg/dL), corrected Ca (8.4–10 mg/dL), and intact parathyroid hormone (PTH) (60–180 pg/mL)⁽³⁾. Lym-pack TA1[®] (Nipro Corporation, Tokyo Japan) was used as dialysate. Electrolyte concentrations (in mEq/L) after preparation of the dialysate were as follows: Na^+ : 138, K^+ : 2.0, Ca^{2+} : 2.5, Mg^{2+} : 1.0, Cl^- : 110, CH_3COO^- : 8, HCO_3^- : 28, and $\text{C}_6\text{H}_{12}\text{O}_6$: 100. Throughout the study period, the dialysate was not changed.

Statistical analysis

All data was expressed as mean \pm standard deviation (SD).

A paired *t*-test was used for before and after comparisons. Where the data were not normally distributed, Wilcoxon signed-rank test was used for analysis.

One-way repeated measures analysis of variance or Friedman's repeated measures analysis of variance by ranks and Tukey's post-hoc test were performed for continuous variables. These statistical analyses were performed using SigmaStat for Windows version 3.5 (Systat Software, Inc. Chicago, USA), and the level of significance was set at 0.05 (2-tailed tests).

Results

A total of 32 patients were evaluated. Background factors, including underlying disease, dosage of SH and CaCO₃, and laboratory results, are shown in Table 1. During the 3-month observation period, no adverse events or reactions, including gastrointestinal symptoms, were reported, and no patients withdrew from this study for any reason. Their average age was 54.8 years (range: 29–72 years). The male-to-female ratio was 22:10. The mean duration of dialysis was 138.1 months (range: 21–354 months).

Results of blood gas analyses are shown in Figure 1. At baseline, the patients showed metabolic acidosis. The mean HCO₃⁻ concentration was 19.9 mEq/L, and the mean optimum HCO₃⁻ level according to the Japanese Society for Dialysis Therapy was 20.65 mEq/L⁽⁸⁾.

Results at 3 months after switching from SH to LaC were compared with those at baseline: pH changed from 7.35 \pm 0.03 to 7.36 \pm 0.03 (*p* = 0.007), HCO₃⁻ from 19.90 \pm 2.03 mEq/L to 20.57 \pm 2.06 mEq/L (*p* = 0.186), and base excess (BE) from -5.13 \pm 2.08 to -4.25 \pm 1.92 (*p* = 0.036); pH and BE changed significantly between baseline and after the changeover, whereas the change in HCO₃⁻ was not significant. Anion Gap increased from 16.6 \pm 2.9 mEq/L to 17.3 \pm 2.3 mEq/L (*p* = 0.2811). Levels of P, Ca and PTH are shown in Figure 2. P was 6.4 \pm 1.4 mg/dL, Ca was 9.3 \pm 0.7 mg/dL, and i-PTH was 156.78 \pm 90.55 pg/mL before the changeover; no significant change was seen in these parameters at the end of the study period.

Changes in electrolyte levels are summarized in Figure 3. K decreased significantly from 5.2 \pm 0.6 mEq/L at baseline to 4.9 \pm 0.6 mEq/L, 3 months after the changeover (*P* = 0.003). Cl also decreased significantly from 102 \pm 4 mEq/L

at baseline to 101 \pm 4 mEq/L by 3 months after the change-over to LaC (*p* = 0.015).

Changes in parameters of lipid metabolism are shown in Figure 4. Total cholesterol had increased significantly at 3 months (from 159 \pm 27 mg/dL to 175 \pm 35 mg/dL; *p* < 0.001), whereas no significant change was seen in the triglyceride level. Total protein and albumin (indicators of nutritional status) were also not significantly different 3 months after the changeover. In addition, no clinically significant gastrointestinal symptoms attributable to SH were reported, and no changes were seen in dietary intake after switching to LaC during this study.

Table 1. Baseline characteristics of hemodialysis patients

		Normal range
Age (years)	54.8 (29-72)	
Sex (male:female)	22 : 10	
Dialysis duration (month)	138.1 (21-354)	
SH dose (mg/day)	3039	
CaCO ₃ dose (mg/day)	1600	
pH	7.35 \pm 0.03	7.380-7.460
HCO ₃ ⁻ (mEq/L)	19.90 \pm 2.03	21.0-29.0
BE	-5.13 \pm 2.08	-2.0-+2.0
Potassium (mEq/L)	5.2 \pm 0.6	3.5-5.0
Chloride (mEq/L)	102 \pm 4	98-108
Adjusted-calcium (mEq/L)	9.3 \pm 0.7	8.2-10.0
Phosphorus (mEq/L)	6.4 \pm 1.4	2.5-4.5
Intact PTH (pg/mL)	156.78 \pm 90.55	10-65
Total-cholesterol (mg/dL)	159 \pm 27	150-219
Triglyceride (mg/dL)	125 \pm 60	50-149
Total protein (g/dL)	6.5 \pm 0.6	6.5-8.2
Albumin (g/dL)	3.9 \pm 0.2	3.7-5.5
Underlying disease		
Chronic glomerulonephritis	19	
Diabetes	4	
Nephrosclerosis	3	
Polycystic kidney	2	
Lupus nephritis	1	
Purpura nephritis	1	
Pyelonephritis	1	
Unknown	1	

Abbreviations: SH, sevelamer hydrochloride; BE, base excess; PTH, parathyroid hormone.

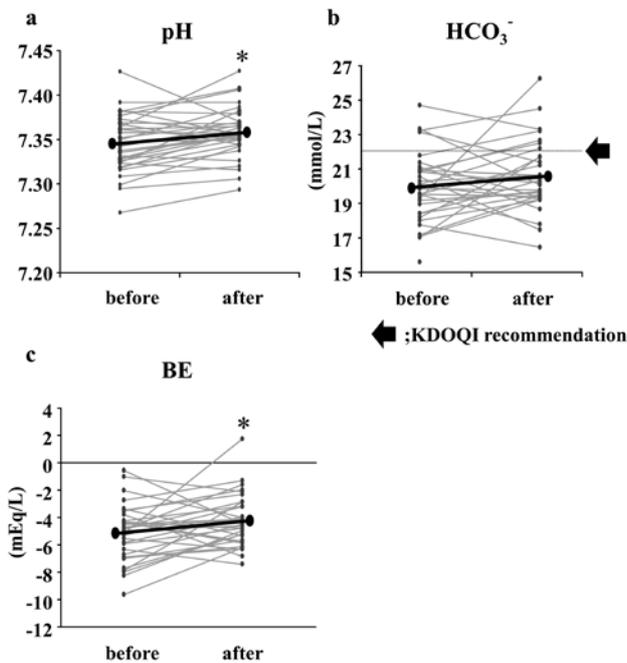


Figure 1. Results of blood gas analyses at 3 months after the changeover from SH to LaC were compared with those at baseline: a; pH changed from 7.35 ± 0.03 to 7.36 ± 0.03 ($p = 0.007$), b; HCO_3^- from 19.90 ± 2.03 mEq/L to 20.57 ± 2.06 mEq/L ($p = 0.186$), c; base excess (BE) from -5.13 ± 2.08 to -4.25 ± 1.92 ($p = 0.036$).

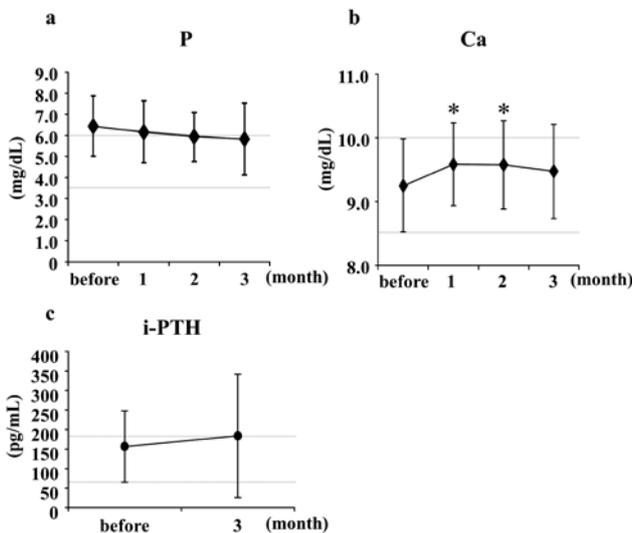


Figure 2. Levels of Ca, P, and intact parathyroid hormone (i-PTH) at 3 months after the changeover from SH to LaC were compared with those at baseline: a; P 6.4 ± 1.4 mg/dL, b; Ca was 9.3 ± 0.7 mg/dL, and c; i-PTH 156.78 ± 90.55 pg/mL before the switch; no significant change was seen in these parameters at the end of the study period.

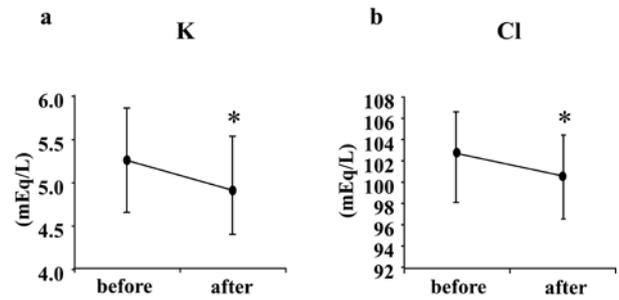


Figure 3. Changes in electrolyte levels are shown. a; K decreased significantly from 5.2 ± 0.6 mEq/L at baseline to 4.9 ± 0.6 mEq/L 3 months after the changeover ($p = 0.003$). b; Cl also decreased significantly from 102 ± 4 mEq/L at baseline to 101 ± 4 mEq/L 3 months after the changeover to LaC ($p = 0.015$).

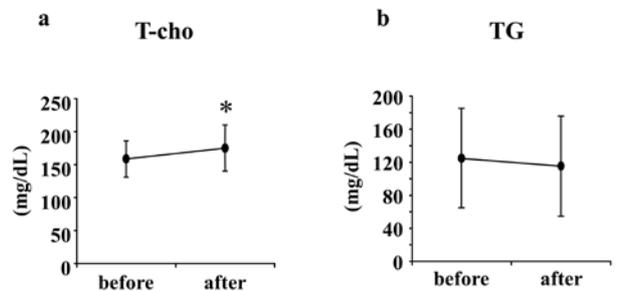


Figure 4. The results of measurement of parameters on lipid metabolism are shown. a; Total cholesterol (T-cho) was increased significantly at 3 months (from 159 ± 27 mg/dL to 175 ± 35 mg/dL; $p < 0.001$), b; no significant change was seen in the triglyceride (TG) level.

Discussion

In this study, we retrospectively evaluated the effects of LaC on metabolic acidosis in hemodialysis patients living in Nagasaki who were obliged to switch from SH to LaC due to the Eastern Japan Great Earthquake Disaster. In the patients in this study, although citrate dialysate was not used, pH and BE increased significantly, and blood HCO_3^- levels increased non-significantly from 19.90 ± 2.03 mEq/L to 20.57 ± 2.06 mEq/L ($p = 0.186$). Furthermore, three months after switching from SH to LaC, K and Cl decreased significantly, probably because these ions moved into the cells as metabolic acidosis was corrected. No serious gastrointestinal side effect was recorded.

SH is a polycationic polymer in the absence of Ca, which is partially in the cationic state in the digestive tract; SH binds to phosphate, released from food in the anionic state, with an ionic or hydrogen bond. These complexes are not absorbed and are excreted in the feces. It is reported that 5

mEq of HCl is released per gram of SH⁽⁶⁾. Therefore, it has been reported that the dose of SH positively correlates with acidosis in a dose-dependent manner. Brezina *et al.* suggested the following as the possible mechanism of acidosis due to the oral administration of SH: 1) SH binds to P, causing release of HCl; 2) SH binds to HCO_3^- , causing release of HCl and reduction in HCO_3^- ; 3) SH binds to bile acid, causing release of HCl⁽⁶⁾. Additionally, SH binds to short chain fatty acids that act as HCO_3^- precursors in the large intestine; these precursors are then eliminated and HCl is released⁽⁹⁾. It is possible that these mechanisms cause the level of HCO_3^- in the body to decrease as the dose of SH is increased.

On the other hand, LaC is a non-Ca-containing phosphate binder, made from the rare earth element La, and is characterized by binding strongly to P to form a complex. Clinical use of LaC was commenced from 2009 in Japan. It has been reported that, in comparison with CaCO_3 , the ability of LaC to eliminate P is 1.5 times higher, that the incidence of hypercalcemia is lower in patients on LaC therapy, and that LaC has a lowering effect on serum P comparable to that of Aluminium preparations⁽¹⁰⁾. Recently, Filiopoulos *et al.* suggested that the improvements in metabolic acidosis are due to effects of LaC on the acid-base balance⁽¹¹⁾. Similarly in our study, the HCO_3^- level showed an upward trend, and the pH and BE were significantly increased at 3 months after switching from SH to LaC.

In our study, pH and BE increased significantly, but no significant increase in blood HCO_3^- levels was noted by switching to LaC. In dialysis patients, the acid-base balance is generally brought to near normal levels by the HCO_3^- received from the dialysate. Furthermore, 53.1% of the patients took sodium bicarbonate with SH in our study. Therefore, the baseline HCO_3^- level might maintain near normal levels not only by the supply from dialysate but also by administration of sodium bicarbonate.

In addition, it is reported that the Cl^- ions contribute less to the acid-base balance in dialysis patients. The patients in our study showed normal Cl^- levels at baseline, despite the presence of SH-produced HCl. On the contrary, it is suggested that albumin, P, and the unmeasured nonvolatile acid play important roles as the plasma buffers in hemodialysis patients⁽¹²⁾. In the present study, we observed that P levels showed a decreasing trend 3 months after treatment change even though we converted SH to the estimated dosage of LaC with same degree of P-lowering effect as previously reported^(13,14). Thus, the decrease of P by LaC might be associated with improvement in metabolic acidosis.

With regard to the effect on lipid metabolism, total cho-

lesterol levels increased significantly after switching to LaC, suggesting that SH might decrease cholesterol levels. This is likely because SH is an anion exchange resin, and decreases the P level through binding to it; moreover, SH also inhibits reabsorption of bile acids by binding to bile acids in the enterohepatic circulation and decreases the level of total cholesterol⁽¹⁵⁾. In fact, it has been reported that SH inhibits progression of coronary artery calcification more effectively than Ca-containing phosphate binders, such as CaCO_3 ⁽⁵⁾. From the viewpoint of prevention of arteriosclerosis, SH can therefore be useful in improving lipid metabolism.

Recently, sevelamer carbonate was developed in Europe and the U.S., in which the hydrochloric acid group was replaced with a carboxyl group, to create a phosphate binder that does not induce acidosis; however, this agent has not yet been approved in Japan. Currently, to treat hyperphosphatemia without exacerbation of metabolic acidosis, SH should be used at the lowest dosage possible, and other phosphate binders added as appropriate.

In conclusion, pH and BE increased significantly, but no significant increase in blood HCO_3^- levels were noted; however the blood HCO_3^- levels showed an increasing trend at 3 months after switching from SH to LaC due to the Eastern Japan Great Earthquake Disaster. On the other hand, total cholesterol levels increased by the change of prescription. However, it is not clear whether the favorable effect of LaC on metabolic acidosis in dialysis patients leads to the long-term benefit for their survival at present. Thus, we hope large-scale clinical studies to investigate the long-term effects of LaC in the future.

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