Phosphate binders and metabolic acidosis in patients undergoing maintenance hemodialysis—sevelamer hydrochloride, calcium carbonate, and bixalomer

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Abstract
The serum bicarbonate (HCO₃⁻) levels are decreased in chronic hemodialysis (HD) patients treated with sevelamer hydrochloride (SH). We assessed the effects of bixalomer on the chronic metabolic acidosis in these patients. We examined 12 of the 122 consecutive Japanese patients with end-stage renal disease on HD, who orally ingested a dose of SH (≥2250 mg), and an arterial blood gas analysis and biochemical analysis were performed before HD. Patients whose serum HCO₃⁻ levels were under 18 mmol/L were changed from SH to the same dose of bixalomer. A total of 12 patients were treated with a large amount of SH. Metabolic acidosis (a serum HCO₃⁻ level under 18 mmol/L) was found in eight patients. These patients were also treated with or without small dose of calcium carbonate (1.2 ± 1.1 g). The dose of SH was changed to that of bixalomer. After 1 month, the serum HCO₃⁻ levels increased from 16.3 ± 1.4 to 19.6 ± 1.7 mmol/L (P < 0.05). Metabolic acidosis was not observed in four patients (serum HCO₃⁻ level: 20.3 ± 0.7 mmol/L) likely because they were taking 3 g of calcium carbonate with SH. In the present study, the development of chronic metabolic acidosis was induced by HCl containing phosphate binders, such as SH, and partially ameliorated by calcium carbonate, then subsequently improved after changing the treatment to bixalomer.

Key words: Bixalomer, calcium carbonate, hemodialysis, lanthanum carbonate, metabolic acidosis, sevelamer hydrochloride

INTRODUCTION
Bommer et al.¹ reported that the state of metabolic acidosis arising due to hemodialysis (HD) is linked to a poorer survival, and it has also been reported to have a negative impact on the bone metabolism in these patients.²,³

The serum bicarbonate (HCO₃⁻) levels decrease in the chronic HD patients with end-stage renal disease (ESRD) treated with sevelamer hydrochloride (SH),⁴ whereas these levels increase with the use of calcium-containing phosphate binders. Administering calcium carbonate (CC) improves metabolic acidosis. Furthermore, the chronic metabolic acidosis induced by SH was mitigated by CC.⁵

Bixalomer,⁶⁷ which is made in Japan (Astellas Pharma Inc., Tokyo) and was discovered in the United States (Ilypsa, Inc., Santa Clara, CA, USA), is a new Ca-free, metal-free, potent phosphate binder, non-hydrochloride,
and nonabsorptive polymer. However, it has been sold only in Japan since June 2012. We herein assessed the effects of bixalomer on the metabolic acidosis.

Although HCO$_3^-$ levels are known to be decreased, it has been unclear whether moderate metabolic acidosis is induced by SH. We therefore investigated the effects of phosphate binders, CC, lanthanum carbonate (LC), SH, and bixalomer on the metabolic acidosis in chronic HD patients.

**METHODS**

**Patient selection**

We performed blood sampling studies in 122 consecutively enrolled patients with ESRD on HD at the Fuku-mitsu Hospital. As shown in Table 1, in 12 patients (male/female 7/5, age: 60 ± 14 years, dialytic age: 11.9 ± 7.3 years) who orally ingested a large dose of SH (dose ≥2250 mg/day, inclusion criteria), an arterial blood gas analysis and serum biochemical analysis were performed before HD. The patients were subgrouped into those with a serum HCO$_3^-$ levels under 18 mmol/L group and those with a serum HCO$_3^-$ levels over 18 mmol/L. The patients whose serum HCO$_3^-$ levels were under 18 mmol/L were changed from SH to the same dose of bixalomer, and the serum HCO$_3^-$ levels were measured 1 month after the change (Figure 1).

The etiology of chronic renal failure was chronic glomerulonephritis in eight patients (male/female: 4/4, IgA nephropathy: 2, others: unknown), diabetic nephropathy in three patients (2/1), and hypertensive nephrosclerosis in

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**Table 1 Patient background**

| CKD group                | All | HCO$_3^-$ ≥ 18 mmol/L | HCO$_3^-$ < 18 mmol/L |
|--------------------------|-----|-----------------------|----------------------|
| n                        | 12  | 4                     | 8                    |
| Age (years)              | 60 ± 14 | 60 ± 14 | 60 ± 15 |
| M/F                      | 7/5 | 3/1                   | 4/4                  |
| Underlying diseases      |     |                       |                      |
| Chronic glomerulonephritis | 8  | 2                     | 6                    |
| Diabetic nephropathy     | 3   | 1                     | 2                    |
| Hypertensive nephrosclerosis | 1 | 1                     | 0                    |
| Phosphate binders        |     |                       |                      |
| Sevelamer hydrochloride  | 3000 ± 123 mg | 2812 ± 718 mg | 3656 ± 2022 mg |
| Calcium carbonate        | 2.0 ± 1.0 g (9) | 3.0 ± 0.0 g (4) | 1.2 ± 1.1 g (5) |
| Lanthanum carbonate      | 1750 ± 433 mg (3) | 1500 mg (1) | 1875 ± 530 mg (2) |
| Vitamin D analogue       |     |                       |                      |
| Alfacalcidol             | 2   | 0                     | 2                    |
| Calcitriol               | 3   | 3                     | 0                    |
| Maxacalcitrol            | 4   | 1                     | 3                    |
| Calcimimetics            |     |                       |                      |
| Cinacalcet hydrochloride | 4   | 1                     | 3                    |

The data are expressed as the means ± standard deviation.

CKD = chronic kidney disease.

*P < 0.05 compared with the HCO$_3^-$ over 18 mmol/L group. ( ); no.

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**Figure 1** A total of 122 patients enrolled in this study.
one patient (0/1). None of these patients had liver or lung disease or exhibited residual diuresis. The nutritional status and daily phosphate balance in the diet were stable.

We concluded a prospective, non-randomized analysis at a single center. The procedures followed were in accord with the ethical standards of the committee on human experimentation of Fukumitsu Hospital.

**Laboratory methods**

The arterial blood gas analysis before HD and during the first week of HD and the analysis of serum sodium, potassium, chloride, adjusted calcium, phosphate, creatinine, blood urea nitrogen, whole parathyroid hormone, and hematocrit levels were performed before HD. The serum anion gap was calculated as [serum sodium level] − ([arterial blood HCO\(_3^−\) level] + [serum chloride level]). The serum calcium level \(×\) serum phosphate product was calculated as [serum adjusted-calcium level] \(×\) [serum phosphate level].

**Dialysis schedule**

The patients underwent 4- to 5-hour sessions of HD therapy three times per week. We used a standard hollow fiber dialyzer and bicarbonate: Na\(^+\) 140 mEq/L, K\(^+\) 2.0 mEq/L, Ca\(^{2+}\) 2.5 mEq/L, Mg\(^{2+}\) 1.0 mEq/L, Cl\(^−\) 110 mEq/L, CH\(_3\)COO\(^−\) 8 mEq/L, HCO\(_3^−\) 30 mEq/L, and glucose 150 mg/dL in Kidney Solution AF-3E (Fuso Pharmaceutical, Co., Ltd., Osaka, Japan). The rate of blood flow was 200 mL/min, and the rate of the dialysate flow was kept constant at 500 mL/min.

**Statistical analysis**

The values were expressed as means ± standard deviation. The changes in the parameters were assessed using unpaired t tests for parametric data between the HCO\(_3^−\) over 18 mmol/L group and the HCO\(_3^−\) under 18 mmol/L group, and paired t tests were used for parametric data between the SH and the bixalomer treatment in the HCO\(_3^−\) under 18 mmol/L group. A value of P < 0.05 was considered to be statistically significant.

**RESULTS**

The 12 chronic HD patients evaluated in this study included seven males and five females. The etiology of the chronic renal failure was chronic glomerulonephritis in nine cases and diabetic nephropathy in three cases. The doses of phosphate binders used were SH, 3000 ± 123 mg; CC, 2.0 ± 1.0 g; and LC, 1750 ± 433 mg. The vitamin D analogues used were alfacalcidol in two cases, calcitriol in three cases, maxacalcitol in four cases, and cinacalcet hydrochloride in four cases (Table 1).

There were four chronic HD patients whose serum HCO\(_3^−\) levels were over 18 mmol/L. There were three males and one female in this group, and they had a mean age of 60 ± 14 years old. Two of these had chronic glomerulonephritis, one had diabetic nephropathy, and one had hypertensive nephrosclerosis (the HCO\(_3^−\) over 18 mmol/L group; Table 1). The doses of phosphate binders used were SH, 2812 ± 718 mg; CC, 3.0 ± 0.0 g; and LC, 1500 mg. Calcitriol was used in three cases, and maxacalcitol was used in one case (Table 1). The clinical data of the patients with ESRD are shown in Table 2. There were no significant differences in the clinical data between the two

| Table 2 | Clinical data of patients with ESRD |
|---------|-----------------------------------|
| CKD group               | All        | HCO\(_3^−\) ≥ 18 mmol/L | HCO\(_3^−\) < 18 mmol/L |
|                     | SH | HCO\(_3^−\) ≥ 18 mmol/L | HCO\(_3^−\) < 18 mmol/L |
|                     | n  | SH | SH                   | SH \(\rightarrow\) bixalomer |
| Hematocrit (%)         | 12 | 33.0 ± 3.0 | 32.0 ± 3.0 | 34.0 ± 4.0 |
| Creatinine (mg/dL)     | 10.2 ± 2.5 | 11.8 ± 2.5 | 8.4 ± 2.3 |
| Blood urea nitrogen (mg/dL) | 56.0 ± 8.0 | 55.0 ± 7.0 | 57.0 ± 9.0 |
| Potassium (mEq/L)      | 4.9 ± 0.5 | 4.9 ± 0.5 | 4.9 ± 0.5 | 4.9 ± 0.5 |
| Adjusted calcium (mg/dL) | 9.2 ± 0.5 | 9.7 ± 0.6 | 9.0 ± 0.4 | 9.1 ± 0.5 |
| Phosphate (mg/dL)      | 5.9 ± 1.4 | 5.8 ± 1.7 | 6.0 ± 1.3 | 5.9 ± 2.0 |
| Adjusted calcium \(×\) phosphate | 54.0 ± 12.0 | 55.0 ± 13.0 | 54.0 ± 12.0 | 54.0 ± 14.0 |
| Whole parathyroid hormone (pg/mL) | 88.0 ± 73.0 | 104.0 ± 73.0 | 56.0 ± 71.0 |

Data are expressed as means ± standard deviation.

CKD = chronic kidney disease; ESRD = end-stage renal disease; SH = sevelamer hydrochloride.
subgroups of patients. The serum HCO$_3$– level was 20.3 ± 0.7 mmol/L, and the serum pH 7.33 ± 0.33 mEq/L in this group (Table 3) and all four patients ingested 3 g of CC (Table 1). This dose of CC was significantly higher than that taken by patients in the HCO$_3$– under 18 mmol/L group (P < 0.05; Table 1).

The other eight chronic HD patients, whose serum HCO$_3$– levels were under 18 mmol/L, consisted of four males and four females, with a mean age of 60 ± 15 years old. Six patients had chronic glomerulonephritis and two had diabetic nephropathy (the HCO$_3$– under 18 mmol/L group; Table 1). The doses of phosphate binders used were SH, 3656 ± 2022 mg; CC, 1.2 ± 1.1 g; and LC, 1875 ± 530 mg. Alfacalcidol was used in two cases and maxacalcitol was used in three cases (Table 1), whereas no vitamin D analogues were taken by the other three patients. The clinical data of the group with ESRD are shown in Table 2. The phosphate binder was changed from SH to the same dose of bixalomer in all eight patients in this group. There were no significant changes in the clinical data following treatment with bixalomer compared with that obtained after patients had been treated with SH (Table 2). Compared with the HCO$_3$– over 18 mmol/L group, the pH and serum HCO$_3$– levels were significantly lower in the HCO$_3$– under 18 mmol/L group (P < 0.05; Table 3).

After 1 month of bixalomer treatment, the serum HCO$_3$– level and/or pH was significantly higher (19.6 ± 1.7 mmol/L or 7.33 ± 0.33) compared with when they had been taking SH (16.3 ± 1.4 mmol/L or 7.29 ± 0.02; P < 0.05; Table 3) in the HCO$_3$– under 18 mmol/L group. The serum anion gap was significantly lower following bixalomer treatment (15.4 ± 2.0 mEq/L) than SH treatment (18.0 ± 2.8 mEq/L, P < 0.05; Table 3) in this group.

No acute or chronic adverse effects were found in the bixalomer group during the follow-up period.

### DISCUSSION

The adverse effects associated with phosphate binders include mineral and bone disorders, cardiovascular risk, and metabolic acidosis. Administering CC was demonstrated to improve the chronic metabolic acidosis induced by SH. In the present study, the effects of bixalomer improved the chronic metabolic acidosis induced by ESRD and SH in chronic HD patients.

The previous clinical data suggested that metabolic acidosis contributes to the mortality and/or hospitalization of the chronic HD patients. Low serum HCO$_3$– levels (HCO$_3$– < 17 mmol/L) were associated with an increased risk of mortality and/or hospitalization.

The phosphate binder was changed from SH to the same dose of bixalomer. As was shown in Table 3 in the present study, the serum HCO$_3$– levels were 19.6 ± 1.7 mmol/L in the HCO$_3$– under 18 mmol/L group after 1 month of bixalomer treatment. There were no differences in the serum chloride levels among the three groups (the SH in the HCO$_3$– over 18 mmol/L group, the SH in the HCO$_3$– under 18 mmol/L group, and the bixalomer in the HCO$_3$– under 18 mmol/L group), but the serum anion gap significantly increased following SH treatment and decreased following bixalomer treatment.

An ideal phosphate binder would meet a number of criteria. Although all of these phosphate binders used are effective, they are also associated with significant side effects, such as chronic metabolic acidosis, in the SH-treated patients. However, bixalomer does not induce metabolic acidosis.

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### Table 3 Results of the arterial blood gas, anion gap, and chloride level in the patients with ESRD

| CKD group | All | HCO$_3$– ≥ 18 mmol/L | HCO$_3$– < 18 mmol/L |
|-----------|-----|----------------------|----------------------|
| n         | 12  | 4                    | 8                    |
| pH        | 7.30 ± 0.03 | 7.33 ± 0.03 | 7.29 ± 0.02<sup>a</sup> | 7.33 ± 0.03<sup>b</sup> |
| PCO$_2$ (mmHg) | 35.0 ± 4.0 | 39.0 ± 4.0 | 34.0 ± 3.0 | 37.0 ± 4.0 |
| PO$_2$ (mmHg) | 107.0 ± 11.0 | 108.0 ± 9.0 | 107.0 ± 12.0 | 101.0 ± 9.0 |
| HCO$_3$– (mmol/L) | 17.6 ± 2.3 | 20.3 ± 0.7 | 16.3 ± 1.4<sup>c</sup> | 19.6 ± 1.7<sup>h</sup> |
| Anion gap (mEq/L) | 17.0 ± 2.8 | 14.9 ± 0.8 | 18.0 ± 2.8 | 15.4 ± 2.0<sup>h</sup> |
| Cl (mEq/L) | 104.0 ± 3.0 | 103.0 ± 3.0 | 104.0 ± 3.0 | 103.0 ± 3.0 |

Data are expressed as means ± standard deviation.
CKD = chronic kidney disease; ESRD = end-stage renal disease; SH = sevelamer hydrochloride.
<sup>a</sup>P < 0.05 the HCO$_3$– under 18 mmol/L group compared with the HCO$_3$– over 18 mmol/L group.
<sup>b</sup>P < 0.05 compared with the SH data in the HCO$_3$– under 18 mmol/L group.
In addition, SH is not an ideal phosphate binder due to its cost and tablet burden. On the other hand, LC, the most recently introduced non-calcium phosphate binder, is effective, well tolerated, and has no negative effects on bone histology.\(^1\) \(^2\) \(^3\) Thus, LC may be an ideal phosphate binder to use in chronic HD patients.

The effects on the serum HCO\(_3^–\) levels are more favorable following treatment with sevelamer carbonate than with SH. For this reason, sevelamer carbonate may eventually replace SH as the phosphate binder of choice for patients who cannot tolerate calcium binders.\(^4\) \(^5\) Furthermore, sevelamer carbonate is as good as SH in terms of hyperphosphatemia control in patients with chronic kidney disease, but with better outcome in terms of the serum HCO\(_3^–\) balance.\(^6\)

Hatakeyama et al.\(^6\) reported that bixalomer was developed to decrease the incidence of adverse gastrointestinal events and constipation, relative to SH, in HD patients. In the present study, both chronic metabolic acidosis and gastrointestinal disorders were completely improved by switching to bixalomer in the HD patients.

High levels of salivary phosphate secretion were observed in the HD and chronic kidney disease patients, in association with the intake of serum phosphorus and high-phosphate beverages in the HD patients.\(^7\) It is important that the beverages consumed by HD patients include a high content of phosphate. Additional studies are needed to evaluate the long-term data.

Only eight patients with serum HCO\(_3^–\) levels under 18 exhibited an improvement for 1 month, with a small power for the statistical analysis and clinical investigation. It is critical to discuss the limitations of this study. However, all eight severe acidotic patients improved after switching to bixalomer.

In conclusion, in the present study, chronic metabolic acidosis and ESRD were induced by HCl containing phosphate binders, such as SH, and partially ameliorated by CC, then subsequently improved after changing the treatment to bixalomer. Further studies are ongoing to define the indications for using bixalomer for the management of the serum HCO\(_3^–\) levels. We firmly believe that bixalomer may also be an ideal phosphate binder for the treatment of HD patients.

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**REFERENCES**

1. Bommer J, Locatelli F, Satayatham S, et al. Association of predialysis serum bicarbonate levels with risk of mortality and hospitalization in the Dialysis Outcome and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2004; \(44\):661–671.

2. Williams AJ, Dittmer ID, McAley A, Clarke J. High bicarbonate dialysate in haemodialysis patients: Effects on acidosis and nutritional status. Nephrol Dial Transplant. 1997; \(12\):2633–2637.

3. Lin SH, Lin YF, Chin HM, Wu CC. Must metabolic acidosis be associated with malnutrition in haemodialysed patients? Nephrol Dial Transplant. 2002; \(17\):2006–2010.

4. De Santo NG, Frangiosa A, Anastasio P, et al. Sevelamer worsens metabolic acidosis in hemodialysis patients. J Nephrol. 2006; \(19\)(Suppl 9):S108–S114.

5. 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.

6. Akizawa T, Kameoka T. Long-term treatment of bixalomer in chronic kidney disease patients on hemodialysis with hyperphosphatemia. (abstract). ASN Kidney Week 2011, FR-PO1667, J Am Soc Nephrol. 2011; \(22\):S01A.

7. Akizawa T, Kinugasa H, Kameoka T. A phase III, sevelamer HCl-controlled study of bixalomer in chronic kidney disease patients on hemodialysis with hyperphosphatemia. (abstract). ASN Kidney Week 2011, FR-PO1669, J Am Soc Nephrol. 2011; \(22\):S04A.

8. Albaaj F, Hutchison AJ. Lanthanum carbonate for the treatment of hyperphosphataemia in renal failure and dialysis patients. Expert Opin Pharmacother. 2005; \(6\):319–328.

9. Brezina B, Qunibi WY, Nolan CR. Acid loading during treatment with sevelamer hydrochloride mechanisms and clinical implication. Kidney Int. 2004; \(66\):S39–S45.

10. Wrong OM, Harland CE. Sevelamer-induced acidosis. Kidney Int. 2005; \(67\):776–777.

11. Joy MS, Finn WF; LAM-302 Study Group. Randomized, double-blind, placebo-controlled, dose-titration, phase III study assessing the efficacy and tolerability of lanthanum carbonate: A new phosphate binder for the treatment of hyperphosphatemia. Am J Kidney Dis. 2003; \(42\):96–107.

12. Hutchison AJ, Maes B, Vanwilleghem J, et al. Efficacy, tolerability, and safety of lanthanum carbonate in
13 Shigematsu T; Lanthanum Carbonate Group. Multicenter prospective randomized, double-blind comparative study between lanthanum carbonate and calcium carbonate as phosphate binders in Japanese hemodialysis patients with hyperphosphatemia. *Clin Nephrol*. 2008; 70:404–410.

14 Pai AB, Sherpler BM. Comparison of sevelamer hydrochloride and sevelamer carbonate: Risk of metabolic acidosis and clinical implications. *Pharmaco therapy*. 2009; 29:554–561.

15 Savica V, Santoro D, Monardo P, Mallamace A, Bellinghieri G. Sevelamer carbonate in the treatment of hyperphosphatemia in patients with chronic kidney disease on hemodialysis. *Ther Clin Risk Manag*. 2008; 4:821–826.

16 Hatakeyama S, Murasawa H, Narita T, et al. Switching hemodialysis patients from sevelamer hydrochloride to bixalomer: A single-center, non-randomized analysis of efficacy and effects on gastrointestinal symptoms and metabolic acidosis. *BMC Nephrol*. 2013; 14:222–228.

17 Savica V, Calo LA, Monardo P, et al. Salivary phosphorus and phosphate content of beverages: Implication for the treatment of uremic hyperphosphatemia. *J Ren Nutr*. 2009; 19:69–72.