

Sevelamer Hydrochloride Exacerbates Metabolic Acidosis in Hemodialysis Patients, Depending on the Dosage

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Abstract: Sevelamer hydrochloride, as a phosphate binder that contains neither aluminum nor calcium, is expected to improve the prognosis of dialysis patients. However, sevelamer hydrochloride has been reported to lower the serum bicarbonate level. In the present study, we performed a retrospective study on the potential influences of sevelamer hydrochloride on metabolic acidosis in hemodialysis patients. The subjects were 72 patients who underwent hemodialysis at our hospital. Thirty-six patients taking sevelamer hydrochloride and 36 patients matched for sex, diabetes mellitus, age and duration of dialysis who were not taking sevelamer hydrochloride were studied. We assigned the 36 patients who had been taking sevelamer hydrochloride to the 'sevelamer group', and the 36 patients not taking sevelamer hydrochloride were the control group. Statistical significance was evaluated by a *t*-test and Pearson's correlation coefficient. In the sevelamer group, the mean levels

of bicarbonate, base excess and pH decreased significantly after administration, compared with the values before administration, but in the control group, aggravation of acidosis was not seen. The levels of bicarbonate, base excess and pH after the medication of sevelamer hydrochloride were found to be significantly and negatively correlated with the daily dose of sevelamer hydrochloride. The levels were also found to be significantly and negatively correlated with the cumulative dose of sevelamer hydrochloride; however, the value of the mean levels of chlorine and the anion gap did not increase with sevelamer hydrochloride. Sevelamer hydrochloride caused metabolic acidosis in a dose-dependent manner in hemodialysis patients without hyperchloremia. **Key Words:** Bicarbonate, Hemodialysis, Metabolic acidosis, Non-anion gap acidosis, Sevelamer hydrochloride.

Hyperphosphatemia often occurs in dialysis patients, causing cardiovascular calcification and 2-hyperparathyroidism, which remarkably impair the prognosis of dialysis patients and their quality of life (1,2). Sevelamer hydrochloride is expected to improve the prognosis of dialysis patients as a phosphate binder that contains neither aluminum nor calcium. Since it has been reported that sevelamer inhibits the progression of coronary and aortic calcification in hemodialysis patients (3-5), it is increasingly expected that the use of sevelamer can improve the prognosis of dialysis patients.

On the other hand, it is pointed out that sevelamer hydrochloride reduces the serum bicarbonate (HCO_3^-) level (6,7). Since metabolic acidosis is an important risk factor for the prognosis of dialysis patients, special care should be taken during treatment (1,8,9). Nevertheless, the causal relationship of sevelamer hydrochloride itself and metabolic acidosis has not been well documented.

In the present study, we performed a retrospective study on the potential influences of sevelamer hydrochloride on metabolic acidosis in hemodialysis patients in our hospital. We compared and examined the difference between the data from February 2003 (before sevelamer hydrochloride was marketed in Japan) and the data from February 2005 (when the daily dose of sevelamer hydrochloride reached a plateau) in our hospital.

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TABLE 1. Clinical characteristics of patients

Group	Sevelamer group	Control group	P-value
Number of patients	36	36	
Male/female	22/14	22/14	NS
DM/non-DM	5/31	5/31	NS
Age (years)	57.4 ± 8.4	59.5 ± 8.8	NS
Duration of dialysis (years)	14.9 ± 9.8	14.9 ± 9.9	NS
Dose of sevelamer hydrochloride (mg/day)	3243.1 ± 1476.6	0	
Dose of calcium carbonate (mg/day)	1514.3 ± 1127.8	1772.2 ± 1010.3	NS

Continuous variables are expressed as mean ± SD. DM, diabetes mellitus.

PATIENTS AND METHODS

Patients

The subjects engaged in this study consisted of 72 patients who had been treated with chronic maintenance hemodialysis using high performance dialyzers in our hospital since December 2002 or earlier. All patients were dialyzed three times a week for 3–5 h each time. We assigned 36 patients who had been taking sevelamer hydrochloride for three months or longer at the time of examination in February 2005 to the 'sevelamer group'—patients whose daily dose of sevelamer hydrochloride was altered during these three months were excluded as subjects. In order to make comparisons with the sevelamer group, 36 patients who were not taking sevelamer hydrochloride were assigned as the control group after matching for sex, diabetes mellitus, age and duration of dialysis (Table 1).

Sevelamer hydrochloride and calcium carbonate were used as a phosphate binder. These patients took sevelamer hydrochloride just before meals and calcium carbonate just after meals. Marketing of sevelamer hydrochloride in Japan began in June 2003. From this time, we started administration of sevelamer hydrochloride to a small number of patients with hyperphosphatemia in small quantities of 750 or 1500 mg/day at the beginning and increased the dose gradually while checking for adverse drug reaction. When a sufficient dose of sevelamer hydrochloride had been prescribed for some patients, the dose of calcium carbonate was decreased suitably. The number of patients administered sevelamer hydrochloride gradually increased. In this way, after more than one year the personal daily dose of sevelamer hydrochloride reached a steady level; the dose was 1500–6000 mg/day. Our target points for bone metabolism were the same as the target points of the Kidney Disease Outcomes Quality Initiative (KDOQI) (8), which were:

- serum P 3.5–5.5 mg/dL
- serum Ca 8.4–9.5 mg/dL

- serum intact-parathyroid hormone (PTH) 150–300 pg/mL
- serum Ca × P <55 (mg/dL)².

Laboratory test results

Data was obtained from the periodic examinations in which blood gas analysis were performed three times per year (February, June and October) in all hemodialysis patients at our hospital. To compare the data before and after the administration of sevelamer hydrochloride, we examined the data in February 2003 (before sevelamer hydrochloride came onto the market in Japan) and those in February 2005. In order to avoid any influence by changes in the data based on season, the data from February was adopted for both years. Data in February 2004 was not adopted because the dose of sevelamer hydrochloride was carefully increased gradually and the daily dose was not stable at that time. We then studied the correlation between the dose of sevelamer hydrochloride and the test results in 2005.

Blood samples were collected before the first dialysis of the week using the arterial side of the hemodialysis circuit. All patients investigated provided us with arterial blood samples from the arterio-venous vascular access.

The parameters of blood gas analysis were measured using an automatic pH/blood gas analyzer (Bayer 850, Bayer Healthcare, Tarrytown, NY, USA). The anion gap (AG) was calculated using the formula: $AG = Na^+ + K^+ - (Cl^- + HCO_3^-)$ (Eqn 1).

Statistical analysis

The measured parameters are indicated as mean ± SD. Statistical significance was evaluated using a paired *t*-test. The correlation between the dose of sevelamer hydrochloride and the measured parameters were evaluated by Pearson's correlation coefficient and simple regression analysis. For all analyses, the statistically significant level was set at $P < 0.05$.

TABLE 2. Significant differences between the parameters before and after administration of sevelamer hydrochloride

Group	Parameter	2003 results	2005 results	P-value	
Sevelamer group (n = 36)	HCO ₃ ⁻ (mmol/L)	19.05 ± 1.69	17.61 ± 1.59	<0.001	
	BE (mmol/L)	-6.258 ± 1.837	-8.042 ± 1.807	<0.0001	
	pH	7.326 ± 0.038	7.298 ± 0.036	<0.001	
	pO ₂ (mm Hg)	98.59 ± 18.39	96.80 ± 12.47	NS	
	pCO ₂ (mm Hg)	37.35 ± 3.71	36.82 ± 3.17	NS	
	AG (mmol/L)	24.34 ± 3.46	24.16 ± 2.00	NS	
	Cl (mmol/L)	102.3 ± 2.6	102.9 ± 2.5	NS	
	P (mg/dL)	6.86 ± 1.39	6.05 ± 1.31	<0.01	
	Ca (mEq/L)	9.84 ± 0.68	9.51 ± 0.85	<0.05	
	i-PTH (pg/mL)	298.7 ± 240.1	307.8 ± 171.3	NS	
	T chol (mg/dL)	177.3 ± 39.4	160.3 ± 28.1	<0.01	
	Albumin (g/dL)	3.87 ± 0.34	3.84 ± 0.24	NS	
	Control group (n = 36)	HCO ₃ ⁻ (mmol/L)	19.14 ± 1.76	18.94 ± 1.81	NS
		BE (mmol/L)	-5.897 ± 2.112	-6.389 ± 2.210	NS
pH		7.337 ± 0.052	7.324 ± 0.048	NS	
pO ₂ (mm Hg)		94.82 ± 14.40	99.90 ± 12.17	NS	
pCO ₂ (mm Hg)		36.58 ± 4.18	37.29 ± 3.89	NS	
AG (mmol/L)		22.62 ± 3.13	23.81 ± 3.27	NS	
Cl (mmol/L)		101.6 ± 2.7	101.2 ± 2.6	NS	
P (mg/dL)		5.68 ± 1.51	5.39 ± 1.20	NS	
Ca (mEq/L)		9.03 ± 1.05	8.92 ± 0.98	NS	
i-PTH (pg/mL)		195.1 ± 131.5	186.9 ± 155.0	NS	
T chol (mg/dL)		180.8 ± 44.7	177.7 ± 41.6	NS	
Albumin (g/dL)		3.903 ± 0.319	3.822 ± 0.363	NS	

Data are mean ± SD. AG, anion gap; BE, base excess; Ca, calcium; Cl, chlorine; HCO₃⁻, bicarbonate; i-PTH, intact-parathyroid hormone; P, phosphorus; pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen; T chol, total cholesterol.

RESULTS

Changes before and after the administration of sevelamer hydrochloride

In the sevelamer group, metabolic acidosis was exacerbated and the mean levels of HCO₃⁻, base excess (BE) and pH decreased significantly. Values of the AG had already been high, even before the administration of sevelamer hydrochloride, and were not altered significantly, regardless of the exacerbation of metabolic acidosis.

The mean levels of pO₂ and pCO₂ were within normal limits and did not change significantly. The mean level of chlorine tended to rise slightly, although the rise was not significant. The mean levels of P, Ca and total cholesterol decreased significantly. The mean levels of intact-PTH and albumin did not change significantly.

In the control group, the mean levels of these parameters did not change significantly and aggravation of metabolic acidosis was not seen (Table 2).

Hyperchloremia (serum chlorine level > 109 mEq/L) was not seen in either group.

Correlation between the daily dose of sevelamer hydrochloride and the various parameters of acidosis

The correlation of the parameters in 2005 and the prescribed daily dose of sevelamer hydrochloride

were examined in the sevelamer group. The levels of HCO₃⁻, BE and pH were significantly and negatively correlated with the daily dose of sevelamer hydrochloride. By contrast, the level of chlorine was significantly and positively correlated with the daily dose of sevelamer hydrochloride. There was no correlation between the daily dose of sevelamer hydrochloride and the levels of pCO₂ or AG (Fig. 1).

We defined Δ parameter = (parameter in 2005) - (parameter in 2003) (Eqn 2).

The correlation of the Δ parameters and the prescribed daily dose of sevelamer hydrochloride was examined in the sevelamer group. The levels of Δ HCO₃⁻, Δ BE and Δ pH were significantly and negatively correlated with the daily dose of sevelamer hydrochloride. By contrast, the level of Δ chlorine was significantly and positively correlated with the daily dose of sevelamer hydrochloride. There was no correlation between the daily dose of sevelamer hydrochloride and the levels of Δ pCO₂ or Δ AG (Fig. 2).

There was no correlation between the daily dose of calcium carbonate and the level of HCO₃⁻ after the administration of sevelamer hydrochloride. Similarly, the difference between the daily dose of calcium carbonate between 2003 and 2005 had no correlation with the level of HCO₃⁻ after the administration of sevelamer hydrochloride (data not shown).

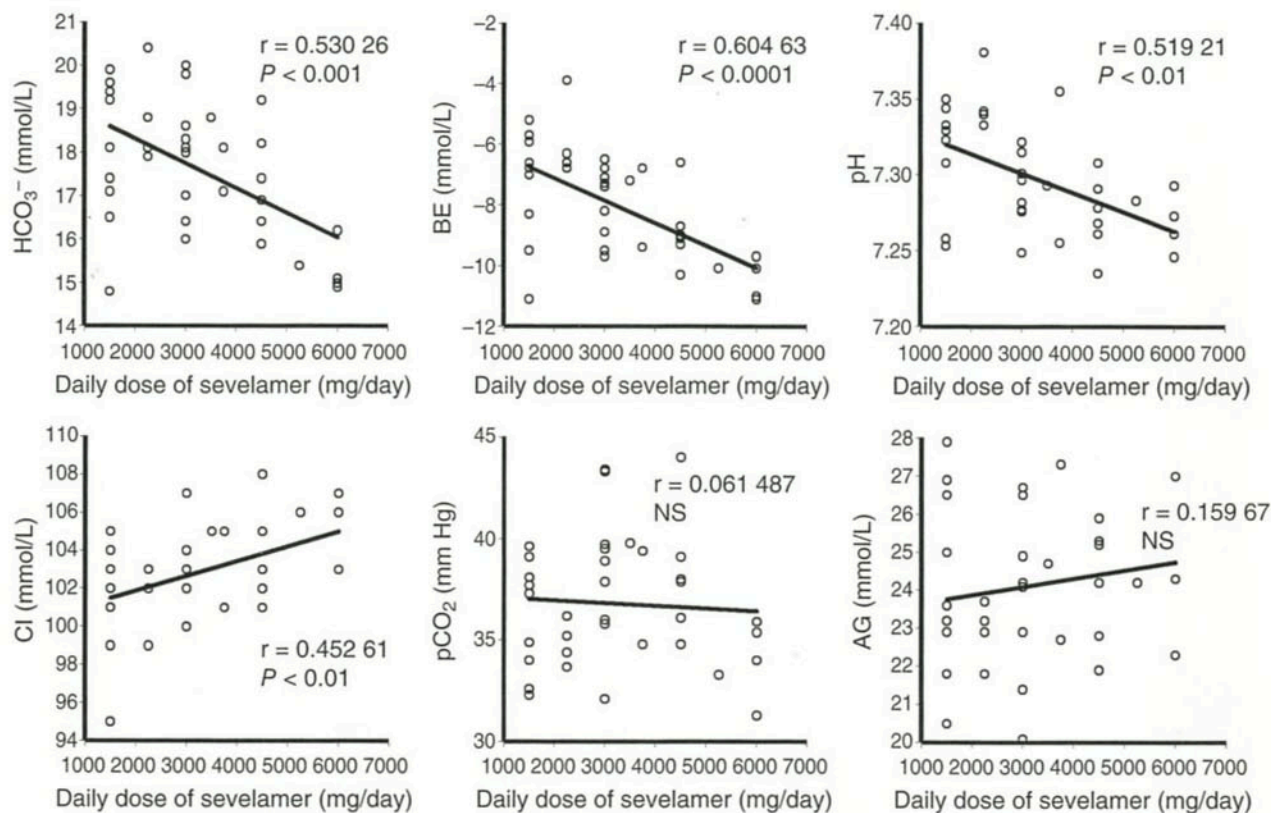


FIG. 1. Correlations between the daily dose of sevelamer hydrochloride and the parameters in 2005 ($n = 36$). AG, anion gap; BE, base excess; Cl, chlorine; HCO_3^- , bicarbonate; pCO_2 , partial pressure of carbon dioxide.

Correlation between the total cumulative dose of sevelamer hydrochloride and the various parameters of acidosis

Next, the correlation of the parameters in 2005 and the total cumulative dose of sevelamer hydrochloride were examined in the sevelamer group, because the cumulative dosages may be more important than the daily dosages. The levels of HCO_3^- , BE and pH were significantly and negatively correlated with the cumulative dose of sevelamer hydrochloride (HCO_3^- : $r = 0.472\ 37$, $P < 0.01$; BE: $r = 0.506\ 76$, $P < 0.01$; pH: $r = 0.383\ 25$, $P < 0.05$). By contrast, the level of chlorine was not significantly correlated with the cumulative dose of sevelamer hydrochloride. There were no correlations between the cumulative dose of sevelamer hydrochloride and the levels of pCO_2 or AG.

Although the levels of ΔBE and ΔpH were significantly and negatively correlated with the cumulative dose of sevelamer hydrochloride, the level of ΔHCO_3^- was negatively, but not significantly, correlated with the cumulative dose of sevelamer hydrochloride (BE: $r = 0.419\ 87$, $P < 0.05$; pH: $r = 0.370\ 31$, $P < 0.05$). The levels of $\Delta\text{chlorine}$, ΔpCO_2 and ΔAG were not significantly correlated with the cumulative dose of sevelamer hydrochloride.

Percentage of patients with severe metabolic acidosis at alert levels

The percentage of patients with a HCO_3^- level of 17.0 mEq/L or lower increased remarkably from 13.9% (5 out of 36) in 2003 to 36.1% (13 out of 36) in the sevelamer group, but did not change in the control group: 11.1% (4 out of 36) in both 2003 and 2005 (Fig. 3).

Patients with subjective symptoms of metabolic acidosis

Hyperventilation appeared in two patients with bicarbonate levels of 15.0 and 15.1 mmol/L without any other reasons for hyperventilation in four cases administered sevelamer hydrochloride at 6000 mg/day. One patient experienced a critical feeling of general fatigue. By stopping sevelamer hydrochloride and the administration of NaHCO_3 , the feeling of general fatigue improved, although the feeling of general fatigue during laborious work was prolonged.

DISCUSSION

Regarding the danger of metabolic acidosis, a multi-institute research study by Edmung et al. has

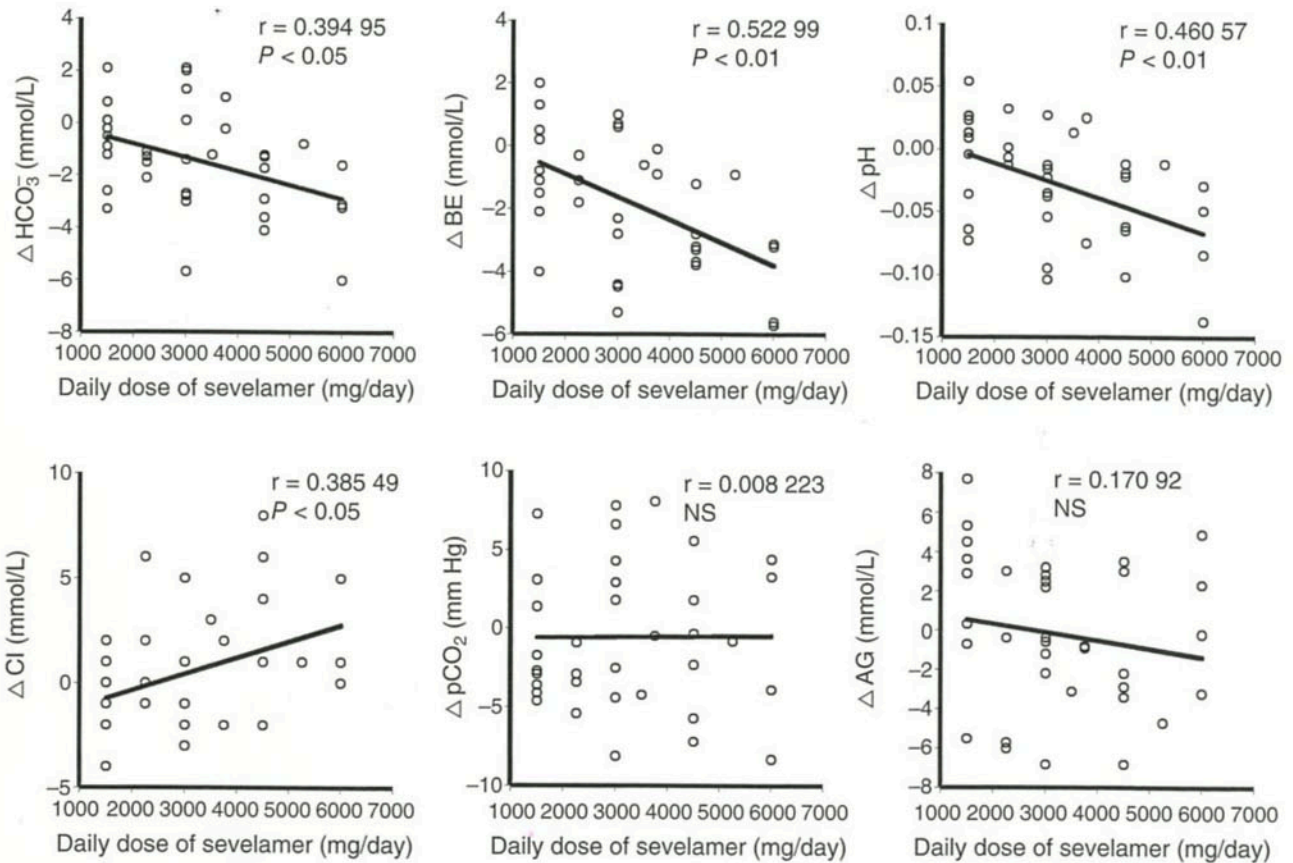


FIG. 2. Correlations between the daily dose of sevelamer hydrochloride and Δ parameters ($n = 36$). $\Delta\text{HCO}_3^- = (\text{HCO}_3^- \text{ data in 2005}) - (\text{HCO}_3^- \text{ data in 2003})$; $\Delta\text{BE} = (\text{BE data in 2005}) - (\text{BE data in 2003})$; $\Delta\text{pH} = (\text{pH data in 2005}) - (\text{pH data in 2003})$; $\Delta\text{Cl} = (\text{Cl data in 2005}) - (\text{Cl data in 2003})$; $\Delta\text{pCO}_2 = (\text{pCO}_2 \text{ data in 2005}) - (\text{pCO}_2 \text{ data in 2003})$; $\Delta\text{AG} = (\text{AG data in 2005}) - (\text{AG data in 2003})$. AG, anion gap; BE, base excess; Cl, chlorine; HCO_3^- , bicarbonate; pCO_2 , partial pressure of carbon dioxide.

shown that metabolic acidosis, with serum CO_2 below 17.5 mmol/L, is by itself associated with increased risk of death in dialysis patients (1). The KDOQI Clinical Practice Guidelines (8) points out that we should keep the total serum CO_2 level at 22 mmol/L or higher as the standard for dialysis patients. Furthermore, the Dialysis Outcomes and Practice Patterns Study (DOPPS) (9) revealed that both high (>27 mmol/L) and low (≤ 17 mmol/L) serum bicarbonate (total CO_2) levels were associated with increased risks for mortality and hospitalization. Since the blood examinations are carried out at the beginning of the week in dialysis facilities in Japan, our data cannot be compared directly with those of the USA and Europe; however, metabolic acidosis is an important risk factor for dialysis patients.

Since the sevelamer hydrochloride contained chlorine, a decrease in bicarbonate due to chlorine load was anticipated, which was actually reported in many

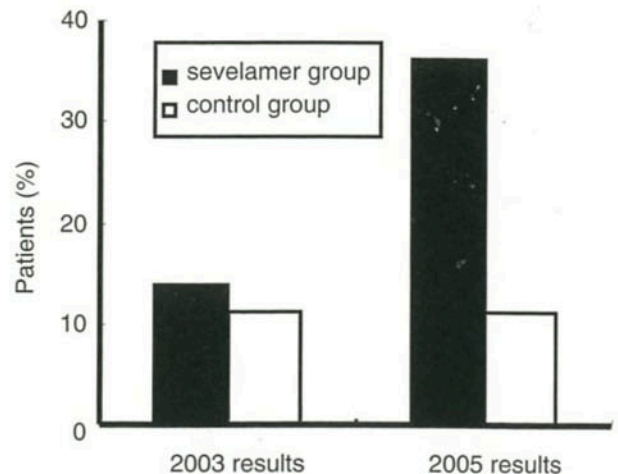


FIG. 3. Percentage of patients with severe metabolic acidosis at the alert level. The percentage of patients with a level of bicarbonate equal to or below 17.0 mEq/L is indicated.

papers (10–13). Many of these reports had pointed out that the decrease in bicarbonate level was caused by the discontinuation of calcium salts rather than by the use of sevelamer hydrochloride, and that the decrease was possibly due to a somewhat transient influence of sevelamer hydrochloride that appeared only at the initial administration.

On the other hand, Brezina et al. reported a hypothetical mechanism underlying the theory that treatment with sevelamer hydrochloride may be a possible acid loading (6). They pointed out a potential mechanism that sevelamer hydrochloride may adsorb not only phosphate and bile acid, but also bicarbonate within the small intestine and emit chlorine. Under such situations, Macrois et al. reported that treatment with sevelamer hydrochloride for 3 months exacerbated metabolic acidosis and induced hyperkalemia in hemodialysis patients (7).

From the time of the appearance of sevelamer hydrochloride in Japan it was pointed out that sevelamer hydrochloride could cause hyperchloremic acidosis. Nevertheless, reports about hyperchloremia caused by sevelamer hydrochloride have not been seen, although some papers reported acidosis caused by sevelamer hydrochloride.

In the present study, a decrease in the levels of not only HCO_3^- , but also base excess and pH were observed significantly and dose-dependently, but the level of chlorine did not increase significantly and the level of chlorine was not significantly correlated with the cumulative dose of sevelamer hydrochloride. In addition, when the patients receiving small quantities (less than 3500 mg/day) of sevelamer hydrochloride were omitted, the level of chlorine increased significantly (from 102.0 ± 2.5 to 104.1 ± 2.2 , $P < 0.05$).

We speculate that the level of chlorine did not increase significantly because it was easily corrected with hemodialysis, even though chlorine was released from sevelamer hydrochloride. Caution is required for metabolic acidosis without hyperchloremia, because the mechanism of acidosis caused by sevelamer hydrochloride is not only from chlorine loading. We consider that sevelamer hydrochloride may directly adsorb bicarbonate within the small intestine as Brezina et al. reported (6), and that metabolic acidosis was exacerbated by the corrected level of serum chlorine.

The AG is used clinically in order to judge the type of metabolic acidosis; its elevation indicates an increasing volume of anion that is not usually measured, which contains sulfuric acid ion, nitric acid ion, lactic acid ion and a ketone body. Although metabolic acidosis was exacerbated after sevelamer hydrochloride medication, the value of the AG did not change.

This shows that non-anion gap acidosis was observed with anion gap acidosis accompanying renal failure, which we have usually observed. Insufficient treatment of chronic renal failure and diabetes mellitus should cause metabolic acidosis with the elevation of the AG. Non-anion gap acidosis is usually observed in disorders due to loss of bicarbonate, such as chronic diarrhea or renal tubular acidosis, and is caused by administration of sevelamer hydrochloride. Therefore, it is strongly suggested that the aggravation of metabolic acidosis observed in the present study was most likely caused by the administration of sevelamer hydrochloride.

Qunibi et al. (13) analyzed the relationship between sevelamer hydrochloride and the serum bicarbonate data as the mean concentration and also as an 'alert level attained' when values were below a threshold of 17 mEq/L, and they revealed that the serum bicarbonate level decreased and that the proportion of patients below 17 mEq/L increased after the administration of sevelamer hydrochloride.

We considered that the cumulative dosages were correlated with metabolic acidosis. However, the daily dosages would be more correlated with metabolic acidosis than the cumulative dosages because the level of ΔHCO_3^- was not significantly correlated with the cumulative dose of sevelamer hydrochloride.

In many dialysis patients, metabolic acidosis had occurred before the administration of sevelamer hydrochloride. Therefore, there is a risk that even slight aggravation will induce critical metabolic acidosis.

Since this examination, we have decreased the quantity of or stopped sevelamer hydrochloride or prescribed sodium bicarbonate for patients whose level of HCO_3^- fell to less than 16 mmol/L.

We speculate that the acidosis caused by sevelamer hydrochloride was not induced by chance, but was dependent on the extent of metabolic acidosis before the administration of sevelamer hydrochloride and on the dose of sevelamer hydrochloride, and it would be exacerbated with chronic administration.

Since the present study is based solely on clinical data, further investigations are necessary to confirm our results.

CONCLUSION

Sevelamer hydrochloride can cause metabolic acidosis in a daily and cumulative dose-dependent manner in hemodialysis patients without the appearance of hyperchloremia.

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