A Review Article: Sevelamer Hydrochloride and Metabolic Acidosis in Dialysis Patients

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Abstract: Sevelamer hydrochloride is a phosphate binder and its effectiveness to reduce the cardiovascular mortality of dialysis patients has been tested. Sevelamer hydrochloride also contains chlorine, so a decrease in bicarbonate due to chlorine load was anticipated and metabolic acidosis thought to associate with sevelamer hydrochloride has been reported in some papers.

We reported that sevelamer hydrochloride exacerbated metabolic acidosis in hemodialysis patients, depending on the dosage. Also a Japanese nationwide survey suggested that sevelamer hydrochloride usage potentially aggravates acidosis in dialysis patients.

A multi-institute research study by Edmung *et al.* has shown that metabolic acidosis, with serum CO2 below 17.5 mmol/L, is by itself associated with increased risk of death in dialysis patients. Furthermore, the Dialysis Outcomes and Practice Patterns Study (DOPPS) revealed that both high (> 27 mmol/L) and low (< or = 17 mmol/L) serum bicarbonate (total CO2) levels were associated with increased risk for mortality and hospitalization.

There has not been any significant evidence to show that sevelamer hydrochloride has reduced the cardiovascular mortality of dialysis patients compared with calcium-based binder.

Clinicians should check not only the level of chlorine but also the level of total CO2 or bicarbonate during the treatment with sevelamer hydrochloride, and control metabolic acidosis.

Key Words: Sevelamer hydrochloride, metabolic acidosis, dialysis, dose depending, prognosis, bicarbonate.

1. DIALYSIS PATIENTS AND SEVELAMER HYDROCHLORIDE

Hyperphosphatemia often occurs in dialysis patients, and it causes cardiovascular calcification and 2-hyperparathyroidism, which remarkably impairs the prognosis of dialysis patients and their QOL [1, 2]. Clinicians had advised patients to avoid foods with high phosphorus content, and some phosphate binders which contain aluminum or calcium were used to control their hyperphosphatemia. But aluminum causes aluminum encephalopathy, and calcium overload causes cardiovascular calcification and associated mortality [3, 4]. Sevelamer hydrochloride was 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 hydrochloride inhibits the progression of coronary and aortic calcification in hemodialysis patients [5-7], it is increasingly expected that the use of sevelamer hydrochloride can improve the prognosis of dialysis patients. So the Kidney Disease Outcomes Quality Initiatives (K/DOQI) guidelines on bone metabolism and disease in chronic kidney disease recommend the use of sevelamer hydrochloride in several common clinical situations [8].

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2. DOES SEVELAMER HYDROCHLORIDE CAUSE METABOLIC ACIDOSIS IN DIALYSIS PATIENTS?

Since sevelamer hydrochloride contains chlorine, a decrease in bicarbonate due to chlorine load (hyperchloremic acidosis) was anticipated. Since metabolic acidosis is an important risk factor for the prognosis of dialysis patients, special care should be taken during treatment [1, 8, 9]. Metabolic acidosis, which was thought to be associated with sevelamer hydrochloride, was actually reported in some papers [10-12]. Nevertheless, the causal relationship of sevelamer hydrochloride itself and metabolic acidosis has not been well documented. Because some 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 [11, 12], and that the decrease associated with sevelamer hydrochloride was possibly due to a somewhat transient influence that appeared only at the initial administration [11].

On the other hand, Brezina *et al.* reported a hypothetical mechanism underlying the theory that treatment with sevelamer hydrochloride may be acid loading [13]. They pointed out a potential mechanism where sevelamer hydrochloride may adsorb not only phosphate and bile acid, but also bicarbonate within the small intestine and emit hydrochloride. Their preliminary data indicated that normal rats treated with sevelamer hydrochloride developed a significant reduction in urine pH, a significant increase in urinary ammonium excre-

1871-529X/08 $55.00+.00

tion, as well as a significant increase in urine calcium excretion. These data support the concept that treatment with sevelamer hydrochloride results in a significant increase in dietary acid load which causes calcium loss and may worsen bone metabolism.

Under such situations, Sonikian *et al.* reported that treatment with sevelamer hydrochloride for 3 months not only exacerbated metabolic acidosis, but also induced hyperkalemia in hemodialysis patients [14, 15]. Hyperkalemia is known to be a cause of the sudden death in hemodialysis patients.

Ramos *et al.* reported about peritoneal dialysis patients that metabolic acidosis (blood bicarbonate levels <22mmol/L) were observed more frequently in patients receiving sevelamer hydrochloride than patients not receiving it (22% vs. 5%, $p<0.01$) [16].

3. SEVELAMER HYDROCHLORIDE EXACERBATES METABOLIC ACIDOSIS IN HEMODIALYSIS PATIENTS, DEPENDING ON THE DOSAGE.

We recently performed a retrospective study on the potential influences of sevelamer hydrochloride on metabolic acidosis in hemodialysis patients in our hospital [17]. We assigned 36 patients who had been taking sevelamer hydrochloride as the "sevelamer group", and 36 patients who were not taking sevelamer hydrochloride as the control group. 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).

Aggravation of Metabolic Acidosis After Administration of Sevelamer Hydrochloride

The mean levels of bicarbonate, base excess, and pH decreased significantly after administration, compared with the values before administration, but the mean level of the anion gap did not increase significantly. This was non-anion gap acidosis which 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. The mean level of chlorine tended to rise, although the rise was not significant. On the other hand, aggravation of acidosis was not seen in the control (non-sevelamer) group. Hyperchloremia (serum chlorine level: more than 109 mEq/L) was not seen in either group.

The Daily Dose of Sevelamer Hydrochloride and Metabolic Acidosis

The levels of bicarbonate, base excess and pH after the medication with sevelamer hydrochloride were found to be significantly and negatively correlated with the daily dose of sevelamer hydrochloride. The level of chlorine was also significantly correlated with the daily dose.

The Cumulative Dose of Sevelamer Hydrochloride and Metabolic Acidosis

The levels of bicarbonate, base excess and pH after the medication with sevelamer hydrochloride were also found to be significantly and negatively correlated with the cumulative dose of sevelamer hydrochloride. The level of chlorine was not significantly correlated with the cumulative dose.

These data showed that sevelamer hydrochloride caused metabolic acidosis in a dose-dependent manner in hemodialysis patients. We speculated 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 acidosis would be exacerbated by chronic administration.

Japanese Nationwide Survey Revealed the Relationship Between Sevelamer Hydrochloride and Metabolic Acidosis

A statistical survey of 3932 nationwide hemodialysis facilities was carried out in Japan at the end of 2004, and 3882 facilities (98.73%) responded. The survey revealed that patients who received high doses of sevelamer hydrochloride tended to have a low concentration of arterial blood HCO3- [18]. This suggested that sevelamer hydrochloride usage potentially aggravated acidosis in dialysis patients.

4. CLINICAL SYMPTOMS RELATED TO METABOLIC ACIDOSIS CAUSED BY SEVELAMER HYDROCHLORIDE

In our study, hyperventilation appeared in two patients with bicarbonate levels of 15.0 and 15.1 mmol/l without any other reasons for hyperventilation, and in four cases sevelamer hydrochloride was administered at 6000 mg/day and one of them experienced a critical feeling of general fatigue [17].

Marco *et al.* also reported on one hyperventilation patient with a bicarbonate level of 18 mmol/l (10).

5. METABOLIC ACIDOSIS AND BONE METABOLISM OF DIALYSIS PATIENTS

In 2003 the "Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines for bone metabolism and disease in chronic kidney disease" [8] was published by the National Kidney Foundation. It pointed out that we should keep the total serum CO2 level at 22 mmol/l or higher as the standard for dialysis patients.

The blood examinations are carried out at midweek in the USA and Europe, but they are carried out at the beginning of the week in almost all of the dialysis facilities in Japan, so our data should not be compared directly with those of the USA and Europe. Bicarbonate data was corrected to total CO2 by adding 1.2 mEq/l, and bicarbonate level at the beginning of the week was corrected to midweek values (like the USA and Europe) by adding 1.2 mEq/l (mmol/l) [9]. So the total serum CO2 level at 22 mmol/L was corrected to 19.6 mEq/l of the bicarbonate level in Japan. It was close to the mean level of bicarbonate before administration of sevelamer hydrochloride in our hospital [17].

6. METABOLIC ACIDOSIS AND PROGNOSIS OF DIALYSIS PATIENTS.

Regarding the danger of metabolic acidosis, a multi-institute research study by Edmung *et al.* has shown that metabolic acidosis, with serum CO2 below 17.5 mmol/L, was by itself associated with increased risk of death in dialysis patients [1]. Furthermore, the Dialysis Outcomes and Practice Patterns Study (DOPPS) [9] revealed that both high (> 27 mmol/L) and low (< or = 17 mmol/L) serum bicarbonate (total CO2) levels were associated with increased risk for mortality and hospitalization.

Qunibi *et al.* [12] 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. They also revealed that the serum bicarbonate level decreased and that the proportion of patients below 17 mEq/L increased after the administration 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. In fact bicarbonate level of one female patient in our hospital decreased from 17.9 to 13.9 mEq/L after the administration of sevelamer hydrochloride. She was not examined in our study [17], because she was dialyzed only twice a week.

7. HAS SEVELAMER HYDROCHLORIDE IMPROVED THE PROGNOSIS OF DIALYSIS PATIENTS COMPARED WITH CALCIUM-BASED BINDER?

Clinicians have been administrating sevelamer hydrochloride to the patients in the belief that it would reduce cardiovascular mortality. But it is still a point of controversy whether sevelamer hydrochloride has improved the prognosis of dialysis patients compared with calcium-based binders or not.

In 2004, B. Manns *et al.* [19] pointed out that no randomized trials have documented the impact of sevelamer hydrochloride on survival, hospitalization, or quality of life, but K/DOQI guidelines [8] recommend its use despite limited evidence of clinical effectiveness and without detailed consideration of cost. Subsequently, M. Tonelli *et al.* conducted a comprehensive search to identify all randomized cross-over or parallel group studies comparing sevelamer hydrochloride to any other therapy or placebo. There was no evidence that sevelamer hydrochloride reduced all-cause mortality, cardiovascular mortality, the frequency of symptomatic bone disease or health-related quality of life [20].

Against these researches, Block *et al.* revealed that treatment with sevelamer hydrochloride was associated with a significant benefit of all-cause mortality as compared to the use of calcium-containing phosphate binders (RIND Study) [21]. However the number of patients was only 127, too small for randomized trials, and there was not a significant benefit against cardiovascular mortality. Some other objections raised against the problems in this article were published as letters in "letters to the editor" [22-24].

In the Dialysis Clinical Outcomes Revisited (DCOR) trial, a large, randomized, multicenter, open-label study, Suki *et al.* [25] compared sevelamer hydrochloride and calcium-based binders on all-cause and cause-specific mortality (cardiovascular, infection, and others) in prevalent hemodialysis patients. All-cause mortality rates and cause-specific mortality rates were not significantly different. Only in patients over 65 years of age was there a significant effect of sevelamer hydrochloride in lowering the all-cause mortality rate. Two great limitations of the study were that it was an open-label study and where 46% of the subjects discontinued early.

In a secondary analysis of the DCOR trial using data collection from the Centers for Medicare & Medicaid Services [26], treatment with sevelamer hydrochloride versus calcium-based binders did not affect overall mortality, cause-specific mortality, morbidity, or first or cause-specific hospitalization, but there was evidence for a beneficial effect on multiple all-cause hospitalizations and hospital days.

There was no significant evidence to show that sevelamer hydrochloride has reduced cardiovascular mortality of dialysis patients compared with calcium-based binders at this point. There was a possibility that metabolic acidosis caused by sevelamer hydrochloride had slightly worsened the prognosis of dialysis patients.

8. HOW WE SHOULD CONTROL METABOLIC ACIDOSIS CAUSED BY SEVELAMER HYDROCHLORIDE

In our hospital, we have decreased the quantity or stopped the use of sevelamer hydrochloride or prescribed sodium bicarbonate for patients whose level of HCO3 fell to less than 16 mmol/L (17). We administrated sevelamer hydrochloride to 33 patients, and of that group 14 patients needed the procedure.

T. Akatsuka *et al.* recommended using sevelamer hydrochloride in combination with calcium carbonate in hemodialysis patients, because treatment with calcium carbonate showed some buffering effects. Calcium carbonate acts as a potent alkalizing agent [27].

M. Sonikian *et al.* corrected sevelamer hydrochloride-induced metabolic acidosis aggravation and hyperkalemia in hemodialysis patients by an increase in dialysate bicarbonate concentration [15].

E. Lindley *et al.* corrected metabolic acidosis after conversion from sevelamer hydrochloride to lanthanum carbonate [28].

Sevelamer carbonate is a new anion exchange resin with the same polymeric structure as sevelamer hydrochloride in which carbonate replaces chloride as the anion. A double-blind, randomized, crossover study investigated the effects of sevelamer carbonate and sevelamer hydrochloride. Serum bicarbonate levels increased during sevelamer carbonate treatment. Sevelamer carbonate and sevelamer hydrochloride were equivalent in controlling serum phosphorus and serum

bicarbonate levels increased with sevelamer carbonate [29]. However it is not currently on the market.

CONCLUSION

Metabolic acidosis is an important risk factor for bone metabolism and the prognosis of dialysis patients, and special care for acidosis should be taken during treatment with sevelamer hydrochloride. The Japanese Society of Dialysis Therapy proposed the guidelines for the treatment of secondary hyperparathyroidism [30]. The guidelines also recommend the use of sevelamer hydrochloride, similar to the K/DOQI guidelines, but it did not recommend a routine test for metabolic acidosis. Clinicians should check not only the level of chlorine, but also the level of total CO2 or bicarbonate during treatment with sevelamer hydrochloride and control metabolic acidosis.

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Received: 10 August, 2008 Revised: 15 September, 2008 Accepted: 16 September, 2008