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## Gastrointestinal symptoms after the substitution of sevelamer hydrochloride with lanthanum carbonate in Japanese patients undergoing hemodialysis

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Lanthanum carbonate has the same phosphorus depressant effect as the other phosphorus adsorbents, and is expected to decrease digestive symptom onset such as constipation in Japanese patients undergoing hemodialysis compared to sevelamer hydrochloride. In this study, we investigated the short- and long-term changes in digestive symptoms in these patients after substituting sevelamer hydrochloride with lanthanum carbonate. We studied 16 patients (4 men, 12 women) and evaluated their gastrointestinal symptoms before administration, at the time of administration, and 2, 4, 8, and 12 weeks after administration, using the Gastrointestinal Symptom Rating Scale. In addition, we conducted repeat evaluations 52 weeks after administration for the patients in whom lanthanum carbonate was administered continuously for 52 weeks. Fourteen (87.5 %) out of the 16 patients could tolerate continuous administration for 12 weeks. The constipation score was  $3.21 \pm 1.74$  before administration,  $2.07 \pm 0.83$  2 weeks after administration,  $1.76 \pm 0.83$  4 weeks after administration,  $1.57 \pm 0.56$  8 weeks after administration, and  $1.41 \pm 0.48$  12 weeks after administration. The scores improved significantly 4 weeks after administration ( $p < 0.05$ ) and even 12 weeks after continuous administration. Among the 16 study patients, 9 patients (1 men, 8 women) were received lanthanum carbonate continuously for 52 weeks. The constipation score was  $3.74 \pm 1.92$  at the start of administration,  $1.37 \pm 0.56$  12 weeks after administration, and  $1.85 \pm 0.63$  52 weeks after administration, with significant improvement even 52 weeks after administration ( $p < 0.05$ ). This study shows that substituting sevelamer hydrochloride with lanthanum carbonate improves constipation symptoms in hemodialysis patients from an early stage, which indicates its usefulness in improving constipation symptoms caused by sevelamer hydrochloride.

### 1. Introduction

Hyperphosphatemia is highly prevalent in patients undergoing hemodialysis and is one of the most important risk factors for cardiovascular disease and mortality in these patients (Hruska et al. 2008). The appropriate control of phosphorus and calcium levels in chronic kidney disease patients undergoing hemodialysis, is a new concept in the clinical management of chronic kidney disease-mineral and bone disorder and is intended to improve prognosis (Fukagawa et al. 2013; Uhlig et al. 2010). In most patients, dietary restrictions and thrice-weekly hemodialysis sessions are insufficient to reduce phosphate levels to the treatment goals of the National Kidney Foundation (NKF K/DOQI) (National Kidney Foundation. 2003). Thus, phosphate-binding agents are necessary for dialysis patients with hyperphosphatemia. Currently available therapeutic agents for hyperphosphatemia include calcium-containing phosphate binders, lanthanum carbonate, ferric citrate hydrate, and ion-exchange resins.

Sevelamer hydrochloride is an ion-exchange resin of non-adsorbable hydrogel that reduces serum phosphorus levels.

Sevelamer hydrochloride has been shown to improve prognosis in hemodialysis patients compared to calcium carbonate (Block et al. 2007; Suki et al. 2007). On the other hand, despite an incidence rate of only 7% for constipation with sevelamer hydrochloride overseas (Slatopolsky et al. 1999), an extremely high rate of constipation has been reported in Japan (Hatakeyama et al. 2013). In addition, since the number of tablets, and hence the dose, tends to increase and induce metabolic acidosis (Qunibi et al. 2004; Akatsuka et al. 2008), stable continuous oral dosing is difficult.

Lanthanum carbonate is a non-calcium, metal-containing phosphate binder that reduces serum phosphorus levels by binding to phosphate in the gastrointestinal tract and inhibiting its absorption. Lanthanum carbonate has the same phosphorus depressant effect as other phosphorus adsorbents (Zhang et al. 2013), and has been shown in multiple studies using various dosing regimens to be effective for reducing phosphate levels in hemodialysis patients (Behets et al. 2004). Lanthanum carbonate has few side effects, such as constipation, in Japanese patients; it may have fewer side effects than sevelamer hydrochloride. Consequently, lanthanum carbonate is expected to limit the onset

**Table 1: Demographic profile of the subjects**

	All	12 week	52 week
Total patient no.	16	14	9
Age (Y), mean ± SD	66 ± 9	64 ± 11	61 ± 12
Sex (M/F)	4/12	3/11	1/8
Hemodialysis vintage (M), mean ± SD	129 ± 35	117 ± 49	131 ± 50
Substitution of sevelamer hydrochloride with lanthanum carbonate	9 (56.3)	7 (50.0)	4 (44.4)
Combined use of sevelamer hydrochloride and lanthanum carbonate	7 (43.8)	7 (50.0)	5 (55.6)
Use of other phosphorus agents			
Precipitated calcium carbonate	8 (50.0)	8 (57.1)	7 (77.8)
Use of vitamin D <sub>3</sub>			
Oral alfacalcidol	2 (12.5)	1 (7.1)	1 (11.1)
Intravenous maxacalcitol	9 (56.3)	8 (57.1)	6 (66.7)
Use of cathartic drug			
Sennoside	12 (75.0)	11 (78.6)	8 (88.9)
Powdered rhubarb	6 (37.5)	6 (42.9)	5 (55.6)
Sorbitol	7 (43.8)	4 (33.3)	5 (55.6)
Glycerin enema	1 (6.3)	1 (7.1)	1 (11.1)
Use of cinacalcet	5 (31.3)	4 (33.3)	3 (33.3)

Data provided are the number (%) of patients, unless otherwise indicated.

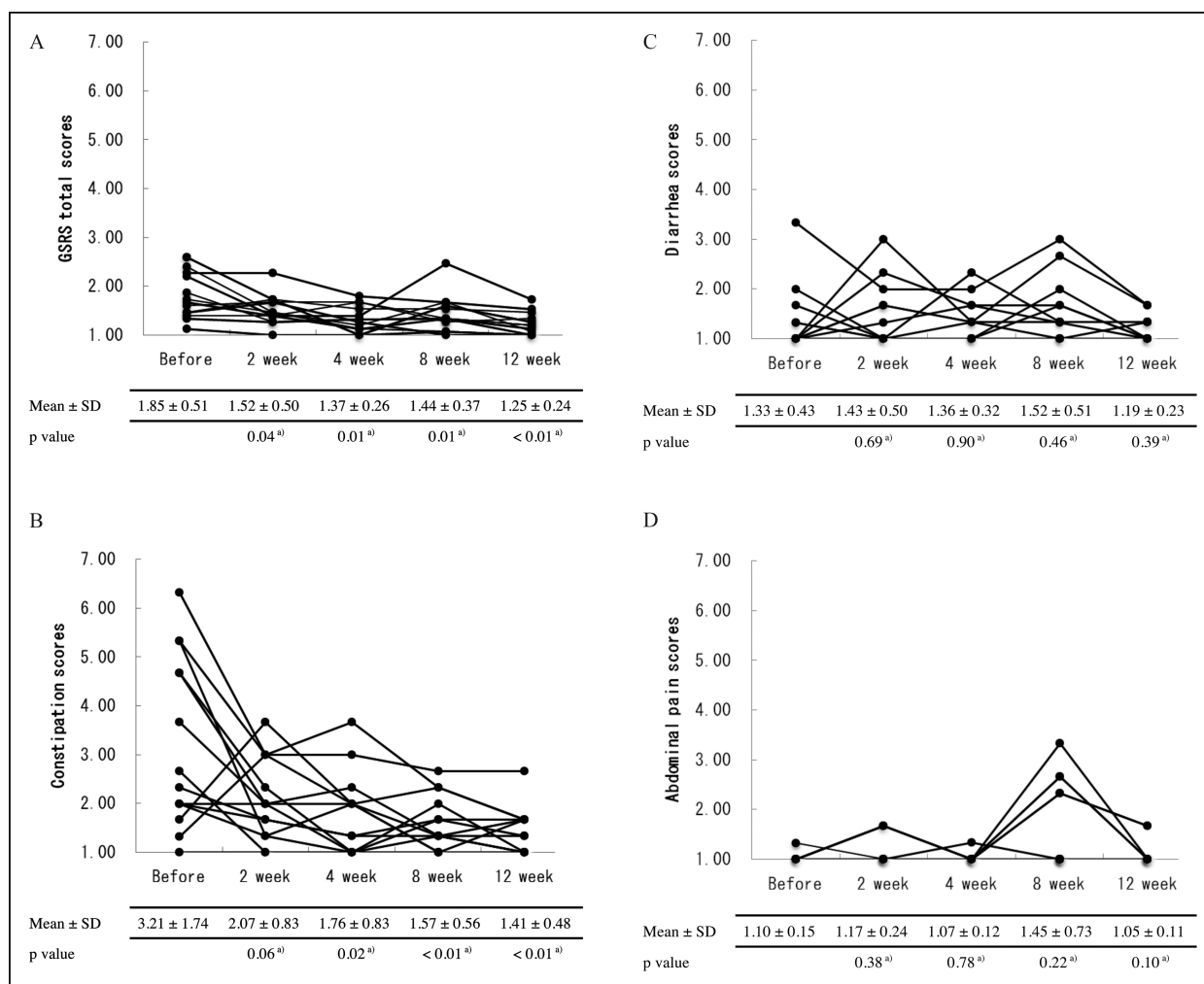


Fig. 1: Changes in each GRS score (short-term evaluation), a. GRS total scores (n = 14), b. Constipation scores (n = 14), c. Diarrhea scores (n = 14), d. Abdominal pain scores (n = 14). <sup>a)</sup>: p values were compared to those before administration and calculated using the paired *t*-test, GRS: Gastrointestinal Symptom Rating Scale.

of digestive symptoms such as constipation, compared to sevelamer hydrochloride.

Whether or not gastrointestinal symptoms are improved after the substitution of sevelamer hydrochloride with lanthanum carbonate is not clear. In this study, we investigated the short and long-term changes in digestive symptoms after substituting sevelamer hydrochloride with lanthanum carbonate.

## 2. Investigations and results

### 2.1. Short-term evaluation

Fourteen (87.5 %) out of 16 patients could tolerate continuous administration of lanthanum carbonate for 12 weeks (Table). The reason for drug withdrawal in 2 patients was diarrheal episodes within 3 days after administration, which were resolved after discontinuation of lanthanum carbonate (sevelamer hydrochloride was re-started). The diarrheal episodes of 2 patients were described as mild; however, lanthanum carbonate was discontinued per patient request. The total Gastrointestinal Symptom Rating Scale (GSRs) score was  $1.85 \pm 0.51$  before administration,  $1.52 \pm 0.50$  2 weeks after administration,  $1.37 \pm 0.26$  4 weeks after administration,  $1.44 \pm 0.37$  8 weeks after administration, and  $1.25 \pm 0.24$  12 weeks after administration. The scores improved significantly 2 weeks after administration ( $p < 0.05$ ) and even 12 weeks after continuous administration (Fig. 1-a). With itemized scores, the constipation score was  $3.21 \pm 1.74$  before administration,  $2.07 \pm 0.83$  2 weeks after administration,  $1.76 \pm 0.83$  4 weeks after administration,  $1.57 \pm 0.56$  8 weeks after administration, and  $1.41 \pm 0.48$  12 weeks after administration. The scores improved significantly 4 weeks after starting administration ( $p < 0.05$ ) and even 12 weeks after continuous improvement (Fig. 1-b). We could not find statistically significant differences in association with other items. We found some cases of temporary worsening of diarrhea scores that improved with lower laxative doses and withdrawal of medications (Fig. 1-c). Although the worsening score periods varied among cases, no tendency was observed. Four cases (29 %) of temporary abdominal pain score worsening were described. In all cases, the abdominal pain score deteriorated in relation to nausea and vomiting, increased with intake of lanthanum carbonate, and occurred in the morning after breakfast (Fig. 1-d). After abdominal pain onset, we lowered the lanthanum carbonate dose, which resulted in improvement in all cases. No adverse effects were noted after discontinuation of administration 2 weeks of treatment.

### 2.2. Long-term evaluation

Among 16 study patients, 9 received lanthanum carbonate consistently for 52 weeks (Table). The reasons for discontinued administration in 2 patients were decreased serum calcium and improved phosphorus levels. Moreover, 3 patients were excluded due to hospitalization of over 1 month during this period. The 9 patients received a stable lanthanum carbonate dose during these 52 weeks. The total GSRs score was  $2.00 \pm 0.57$  before administration,  $1.29 \pm 0.28$  12 weeks after administration, and  $1.30 \pm 0.29$  52 weeks after administration. The scores improved continuously and significantly even 52 weeks after administration ( $p < 0.05$ ) (Fig. 2-a). The GSRs constipation score was  $3.74 \pm 1.92$  at the start of administration,  $1.37 \pm 0.56$  12 weeks after administration, and  $1.85 \pm 0.63$  52 weeks after administration. The scores improved significantly even 52 weeks after administration ( $p < 0.05$ ) (Fig. 2-b). All data are presented as the mean  $\pm$  standard deviation.

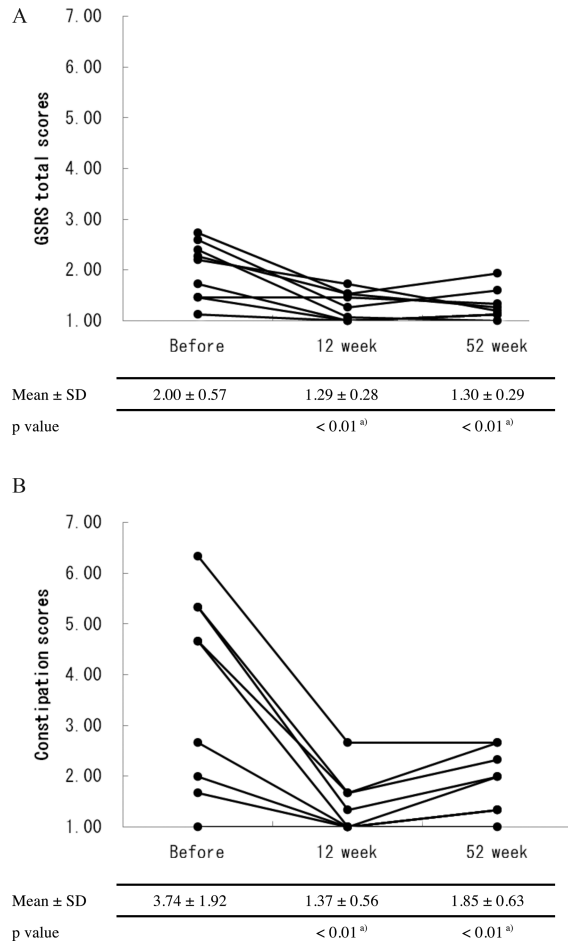


Fig. 2: Changes in each GSRs score (long-term evaluation), a. GSRs total scores (n=9), b. Constipation scores (n=9). <sup>a)</sup>: p values were compared to those before administration and calculated using the paired *t*-test. GSRs; Gastrointestinal Symptom Rating Scale.

### 2.3. Serum phosphorus level and corrected calcium level

We could not find any changes in the serum phosphorus or corrected calcium levels before and after the substitution of medication (Fig. 3). The doses of sevelamer hydrochloride, lanthanum carbonate, and calcium carbonate are shown in Fig. 4, and that of sevelamer hydrochloride was lowered substantially.

## 3. Discussion

The number of tablets for each dose tends to increase in hemodialysis patients, and increasing hyperphosphatemia during the administration of therapeutic medications lowers the quality of life (QOL) in these patients (Slatopolsky et al. 1999). Lanthanum carbonate is required in lower doses compared to sevelamer hydrochloride. According to a previous study, serum phosphorus level was reduced, and the target serum phosphorus level achievement rate improved according to treatment guidelines. Daily dose was reduced by substituting the existing phosphorus adsorbent (sevelamer hydrochloride or lanthanum carbonate) with lanthanum carbonate (Winnie et al. 2010). Our findings are similar to the results of this investigation. We found fewer digestive symptoms such as constipation; however, change in digestive symptoms with the substitution of sevelamer hydrochloride could not be studied. This study has shown that the constipation score improved from an early stage and the effect continues with the substitution of sevelamer hydrochloride with lanthanum carbonate. Therefore, it could improve the QOL of dialysis patients.

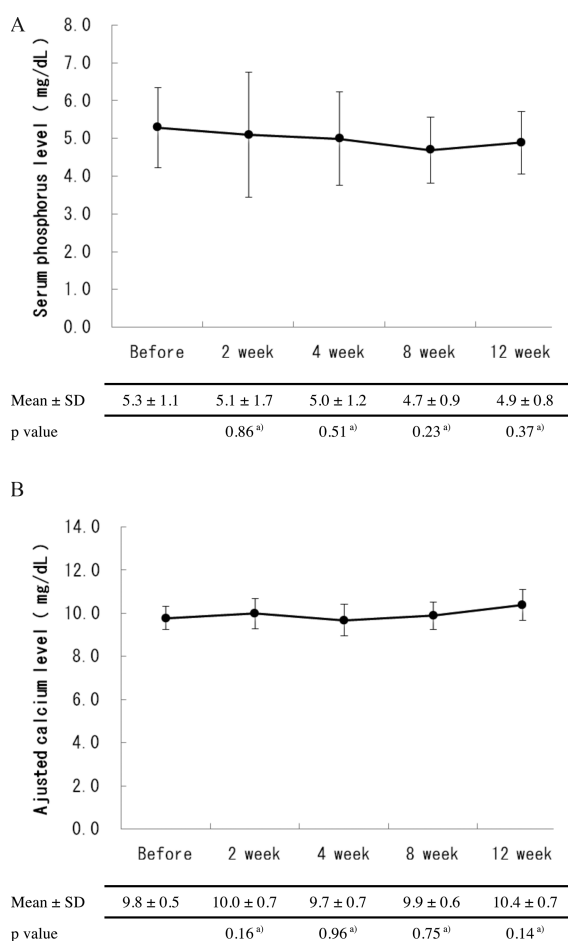


Fig. 3: Changes in laboratory values during the investigation period, a. Serum phosphorus level (n = 14, week before the beginning of hemodialysis), b. Adjusted calcium level (n = 14, week before the beginning of hemodialysis).  
<sup>a)</sup>: p values were compared to those before administration and calculated using the paired *t*-test.

This study has shown that the constipation score for the GRSR in dialysis patients showed a subjective improvement from  $3.21 \pm 1.74$  to  $2.07 \pm 0.83$  within the 2 weeks after substituting sevelamar hydrochloride by lanthanum carbonate. Objective symptom improvement should be evaluated. However, because the dose of the laxative differed according to the type of agent, number of tablets, and administration time for each patient (Table), evaluating changes before and after the substitution were difficult. Other digestive symptoms showed a clear high frequency of onset. Onset time of diarrhea varied among patients; however, we could manage it with the active coordination of laxative dosages. Although, constipation showed gradual improvement with the substitution of sevelamar hydrochloride, diarrheal symptoms were attributed to continuous self-administration of laxative agents for direct intestinal stimulation, such as powdered rhubarb or sennoside. Careful management of stimulant laxative is required for lanthanum carbonate administration.

This study shows that substituting sevelamar hydrochloride by lanthanum carbonate improves constipation symptoms in hemodialysis patients from an early stage, which indicates its usefulness in improving constipation symptoms caused by sevelamar hydrochloride. Appropriate drug administration guidance seems important, because these side effects can be alleviated with proper management of the laxatives at the start of administration.

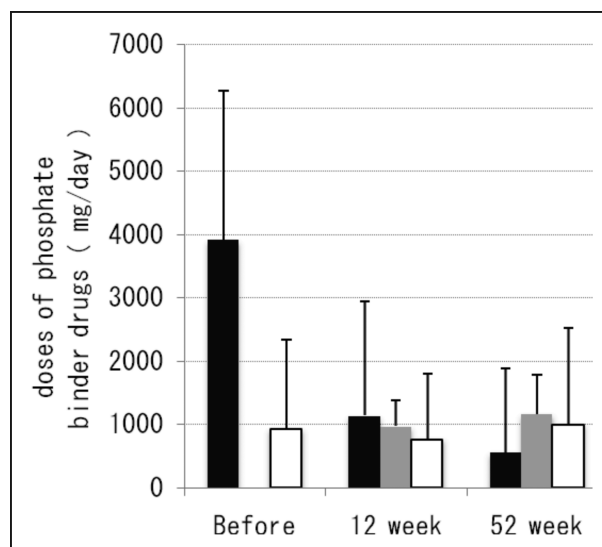


Fig. 4: Changes in the doses of phosphate binder drugs (n=9), ■ Sevelamer hydrochloride, ■ Lanthanum carbonate, □ Calcium carbonate.

## 4. Experimental

### 4.1. Study patients

We included outpatients undergoing dialysis who were prescribed lanthanum carbonate as substitution for sevelamar hydrochloride at Kainan Hospital. We did not set definite exclusion criteria such as age, sex, or dialysis duration. The characteristics of the 16 patients (4 men, 12 women) studied are given in the Table. The investigation period was 12 weeks after starting lanthanum carbonate administration from April to October 2009. To confirm long-term effects, we also investigated 52 months after the start of administration, from April to July 2010. During the period of administration, lanthanum carbonate doses were adjusted based on clinical laboratory test results.

### 4.2. Evaluation method

We conducted evaluations, before administration, at the start of administration, and 2, 4, 8, and 12 weeks after administration using the GSRS (Svedlund et al. 1988). In addition, we conducted evaluations again in patients who received continuous administration for 52 weeks. After blood count and biochemical examinations, the serum phosphorus level before dialysis and the calcium corrected with Payne's formula were investigated.

### 4.3. Statistical methods

Data were examined with paired *t*-tests, and risk rates less than 5% were considered statistically significant.

### 4.4. Consideration of medical ethics

This research was approved by the Institutional Ethics Review Board after consideration of the appropriate medical ethics. We adequately protected each patient's privacy, and obtained oral and written consent.

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