Sevelamer hydrochloride prevents ectopic calcification and renal osteodystrophy in chronic renal failure rats

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Background. Hyperphosphatemia is associated with severe complications, including ectopic calcification of soft tissues, secondary hyperparathyroidism, and renal osteodystrophy (ROD). Sevelamer hydrochloride is a nonabsorbed calcium- and metal-free phosphate binder that lowers serum phosphorus levels in hemodialysis patients. This study examined the efficacy of sevelamer in preventing ectopic calcification of soft tissues and ROD in adenine-induced renal failure rats.

Methods. Male, 12-week-old Wistar-Jcl rats were freely fed an adenine diet (0.75 g adenine in 100 g normal diet) for four weeks. After three weeks of the adenine diet, when serum phosphorus levels had significantly increased, the rats were freely fed a normal diet that contained 1% or 2% of sevelamer for another five weeks. Time course changes of serum levels of phosphorus, calcium, and parathyroid hormone (PTH) were measured. At the end of the study, calcium and phosphorus levels in the heart and aorta were measured, and the calcification of kidney, heart, aorta, and stomach were histopathologically examined. The severity of ROD was evaluated by a histopathologic and morphometric analysis of the femurs.

Results. Compared with the adenine controls (N = 10), the sevelamer-treated (1%, N = 6; and 2%, N = 10) groups of adenine-induced renal failure rats had reduced serum phosphorus, serum calcium × phosphorus product, and serum PTH levels. Moreover, in the treatment groups, sevelamer suppressed calcification of the aorta media, and also the osteoid volume, fibrosis volume, and porosity ratio of femurs.

Conclusion. These results suggest that sevelamer treatment might contribute to the suppression of ectopic calcification and ROD.

In chronic renal failure and dialysis patients, hyperphosphatemia is caused by an accumulation of phosphate resulting from the impaired urinary excretion of phosphate [1, 2]. Dialysis and restriction of dietary phosphate are insufficient to prevent hyperphosphatemia in patients with renal insufficiency [3]. Hyperphosphatemia is associated with severe complications, including ectopic calcification of soft tissues, secondary hyperparathyroidism, and renal osteodystrophy (ROD) [2]. Hyperphosphatemia is accompanied by elevated levels of serum calcium × phosphorus product. Most studies on myocardial, vascular, and coronary artery calcification among end-stage renal disease (ESRD) patients have reported a strong association between calcification and serum phosphorus and/or calcium × phosphorus product levels [4]. Furthermore, secondary hyperparathyroidism induces high turnover bone disease (ROD), which is characterized by an increased activation of osteoblasts and osteoclasts with corresponding elevated rates of bone formation [5–7].

Sevelamer hydrochloride (Renagel®) is a nonabsorbed calcium- and metal-free phosphate binder that lowers the serum phosphorus levels in hemodialysis patients [8–10]. Sevelamer is a hydrogel of crosslinked poly [allylamine hydrochloride], which is completely resistant to digestive degradation and is not absorbed from the gastrointestinal tract. Many benefits have been clinically reported as to the efficacy of lowering the serum phosphorus, calcium × phosphorus product and parathyroid hormone (PTH) levels with minimal effects on serum calcium [8-11]. Recently, it has also been reported that sevelamer plays a role in decreasing the progression of coronary and aortic calcification in hemodialysis patients, possibly by reducing the serum calcium × phosphorus product or serum low-density lipoprotein cholesterol levels [12].

In this study, we examined the effectiveness of sevelamer in preventing the ectopic calcification of soft tissues and ROD in adenine-induced renal failure rats. Our data showed that administration of an adenine diet to rats, resulting in the deposition of 2,8-dihydroxadenine in the renal tubules, induced severe chronic renal failure.

Key words: hyperphosphatemia, phosphate binder, ectopic calcification, renal osteodystrophy, sevelamer hydrochloride, secondary hyperparathyroidism.

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Fig. 1. The experimental design. From day 21 to day 7, adenine diet was administered for the three groups (adenine-administered group, 1% or 2% sevelamer-administered group). At day 7, adenine diet was stopped and after that normal diet was used. At day 0, the administration of sevelamer was started and sevelamer was administered at 1% or 2% mixture diet for 5 weeks.

due to the degeneration of the proximal and distal tubules and interstitial fibrosis [13, 14]. It is also known that this animal model results in hyperphosphatemia related to severe, chronic renal failure [14–16]. This current study demonstrated an increase in ectopic calcification of soft tissues, including the blood vessels, kidney, and muscular layer of the stomach, as well as elevated levels of serum calcium × phosphorus product in adenine-induced renal failure rats. Furthermore, characteristics observed when ROD was induced by hyperparathyroidism in the adenine-induced renal failure rats included osteitis fibrosa, bone resorption cavities, and increased osteoid. The results of this study, with regard to ectopic calcification, are consistent with the effect on sevelamer in a previously published clinical study, and furthermore, these data suggest sevelamer’s potential to prevent the high turnover type of ROD in ESRD patients.

METHODS

Materials

Sevelamer hydrochloride (Renagel®), a crosslinked poly (allylamine hydrochloride), was synthesized by the Dow Chemical Company (Midland, MI, USA) and supplied by Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan). Cellulose was obtained from Sigma Chemical Co. (St. Louis, MO, USA).

Experimental animals

Twelve-week-old male Wistar rats were purchased from Clea Japan, Inc., (Tokyo, Japan). Rats were maintained in sterilized cages and fed standard powder rodent chow containing 1.06% calcium and 1.03% phosphate (CE-2; Clea Japan, Inc.).

Study design

After an acclimatization period of six days, rats were fed a CE-2 diet containing 0.75% adenine, 1.06% calcium, and 0.92% phosphate (adenine diet; Clea Japan, Inc.). The study design is shown in Figure 1. Five rats (the normal-control group) were fed a normal CE-2 diet. After three weeks of the adenine-diet feeding, when serum phosphorus levels significantly increased, the adenine-induced renal failure rats were randomly divided into three experimental groups that were matched with respect to serum phosphorus and creatinine levels: an adenine-control group; a 1% sevelamer-treated group; and a 2% sevelamer-treated group. In order to control the concentrations of sevelamer, it was mixed into a powdered adenine diet or a powdered CE-2 diet. In order to maintain a constant phosphorus concentration in the diet, the diets for the normal-control group and adenine-control group were blended with 2% cellulose, whereas the diet for the 1% sevelamer-treated group was blended with 1% cellulose. The rats were freely fed the adenine diet containing the sevelamer (1% or 2%) for seven days. Then, the adenine diet was changed and the rats were freely fed a normal diet that contained the sevelamer at either 1% or 2% for the next 28 days. Blood samples were collected to analyze the serum parameters on days 7, 21, and 35.

The animals used in this experiment were treated in accordance with Chugai Pharmaceutical’s ethical guidelines of animal care, handling, and termination.

Blood biochemistry

Serum phosphorus, calcium, and creatinine levels were determined with an autoanalyzer (7170-E, Hitachi, Tokyo, Japan). Serum PTH concentrations were determined by using a two-site immunoradiometric assay (IRMA) with the rat PTH IRMA kit (Immutopics, Inc., San Clemente, CA, USA).

Calcium and phosphorus contents in thoracic aorta

At the end of the study, the thoracic aortas were removed and frozen at −20°C until analysis. After lyophilization, using a freeze drier (FD-5N; Tokyo Rikakikai Co., Ltd., Tokyo, Japan), the dried aorta was defatted with chloroform and methanol (2:1) for 48 hours and dehydrated by acetone for three hours. The dried samples were incinerated to ashes at 900°C for 12 hours using an electric muffle furnace (KDF-S90; Denken Co., Ltd., Kyoto, Japan), then extracted with HCl and diluted with distilled water. The levels of calcium and phosphorus in the aorta were determined and represented as the weight of calcium or phosphorus per dry weight of aorta.

Histopathology

Calcification of soft tissues. Aorta, heart, kidney, and stomach were fixed in a 20% neutral-buffered formalin and embedded in paraffin and sectioned by standard methods. The sections were stained using the von Kossa method. Aortas were examined as to the expression of bone matrix proteins osteopontin (monoclonal antibody for osteopontin; LSL Co., Ltd., Tokyo, Japan) and osteocalcin (monoclonal antibody for osteocalcin; LSL Co., Ltd.) by immunohistochemistry.

Renal osteodystrophy in femurs. The left femur was fixed in a 20% neutral-buffered formalin and embedded in paraffin after decalcification and sectioned by standard methods.
methods. The sections were stained with hematoxylin and eosin (HE).

**Morphometrical analysis in ROD**

The right femur was fixed in 70% ethanol and embedded in methyl metacrylate without decalcification. After Villanueva bone staining, cross-sections of the middle femur, 20 to 30 μm thick, were obtained with a cutting and grinding system (BS-3000N, MG-4000; Exakt-Apparatebau, Norderstedt, Germany).

Histomorphometry was performed under fluorescent light microscopy (OPTIPHOT-2; Nikon, Tokyo, Japan) using a semiautomatic, image analyzer system (Bone Histomorphometry, Version 3; System Supply Co., Ltd., Nagano, Japan). For each section, measurements were performed at a magnification of ×156.

Nomenclature, symbols, and units used in this study are those defined in the Report of the American Society for Bone and Mineral Research Nomenclature Committee [17]. Osteoid volume (OV), fibrosis volume (Fb.V), and porosity ratio (Po.Ar/Ct.Ar) were measured as the markers related to ROD.

**Statistical analysis**

Data were expressed as the mean ± standard error (SE). Statistical analysis was performed using the SAS system (SAS Institute, Inc., Cary, NC, USA). An unpaired t test was used to compare the adenine-control group with the normal-control group. The Dunnett multiple comparisons test was used to compare the sevelamer-treated groups with the adenine-control group with regard to the bone histomorphometric data, aorta phosphorus levels, and aorta calcium levels. The Dunnett test, adjusted by the baseline value as the covariate, was used to compare the sevelamer-treated groups with the adenine-control group with regard to the repeated measurements. Serum PTH was analyzed as the logarithmic value of the serum PTH concentration. For histopathology analysis, a Wilcoxon rank-sum test was used to compare the adenine-control group with the normal-control group [8–10]; and with a nonparametric Dunnett test (Steel test) was used to compare the sevelamer-treated groups with the adenine-control group. Statistical significance was defined as \( P < 0.05 \), two-sided.

**RESULTS**

**Serum phosphorus, calcium, calcium \( \times \) phosphorus product, and creatinine levels**

To determine if sevelamer lowers serum phosphorus levels, we used an experimental rat model of adenine-induced renal failure with hyperphosphatemia. The renal
Fig. 6. Effects of sevelamer on aorta calcium and phosphorus contents in adenine-induced renal failure rats. (A) Calcium in aorta was significantly more elevated in the adenine-control group than in the normal-control group. Calcium contents in aorta were significantly decreased in both 1% and 2% sevelamer-treated groups, compared with the adenine-control group. (B) Phosphorus levels in the aorta were significantly more elevated in adenine-control group than that in the normal-control group. Phosphorus levels in the aorta were significantly decreased in both 1% and 2% sevelamer-treated groups compared with the adenine-control group. Data are presented as mean ± SE. #P < 0.05 vs. normal-control group; **P < 0.01 vs. adenine-control group.

Table 1. Effect of sevelamer on calcification of soft tissues

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−, No change; ±, very slight; +, slight; ++, moderate; ++++, severe.

a vs. normal (Wilcoxon rank-sum test)
b vs. adenine control (Steel test)

elevation at day 7 and 21 of treatment before returning to the same level as the normal-control group by the end of the study (Fig. 4). The product was lower at day 7 for both sevelamer 1% and 2%, and also lower at day 21 for sevelamer 2%. As for the serum creatinine, sevelamer did not improve the serum creatinine levels, although there were the tendencies to decrease in all groups after the adenine diet was stopped (Fig. 5).

Ectopic calcification

In order to examine the effectiveness of sevelamer in preventing ectopic calcification of soft tissues, the calcium and phosphorus levels of the thoracic aorta were analyzed, and calcifications of kidney, heart, aorta, and stomach were histopathologically examined by von Kossa staining. In the adenine-control group, the calcium and phosphorus levels of the thoracic aorta were significantly elevated compared to those in the normal-control group and in the sevelamer-treated groups, indicating that sevelamer significantly suppressed an increase in
Fig. 7. Effect of sevelamer on calcification of thoracic aorta. (A to D) von Kossa stains of thoracic aorta of normal-control group (A), adenine-control group (B, C), or 2% sevelamer-treated rat (D) at day 35 after administration. Sevelamer prevented the calcification of aorta media in the adenine-induced renal failure rats. Magnification of (A, B, D), ×2; magnification of (C) ×10.

Fig. 8. Expressions of osteopontin and osteocalcin were observed in calcified regions of thoracic aorta by immunohistochemistry. The aortas of normal rats were negative for osteopontin (A) and osteocalcin (D). The regions of ectopic calcification in adenine-induced renal failure rats were positive for osteopontin (B) and osteocalcin (E). The aortas not expressing ectopic calcification by 2% sevelamer administration were negative for osteopontin (C) and osteocalcin (F). Magnification, ×40.
In this study, it was shown that sevelamer prevented ROD as shown by a decrease in the presence of osteitis fibrosa, porosity in the cortical bone, and osteoid histopathologically in the femurs compared with the adenine-induced renal failure rats (Fig. 10).

When a bone morphometric analysis was performed, the adenine-induced renal failure rats showed changes with regard to ROD, including a significant increase in fibrosis volume, porosity ratio, and osteoid volume (Fig. 11). In the sevelamer-treated groups, all the changes accompanying ROD were significantly improved compared to the adenine-control group.

**DISCUSSION**

Clinically, Renagel® has been reported to contribute to lower serum phosphorus levels in hemodialysis patients [8–10]; and with electron beam tomography (EBT), Renagel® showed suppression of ectopic calcification in the cardiovascular system [12]. In this study, we examined the effectiveness of sevelamer in preventing ectopic calcification of soft tissues histopathologically and biochemically in adenine-induced renal failure rats. Furthermore, a morphometric analysis was used to examine the success of sevelamer in preventing ROD induced by hyperparathyroidism. This study demonstrates that sevelamer, a calcium- and metal-free polymeric phosphate binder, contributes to the prevention of ectopic calcification of soft tissues and ROD by regulating the serum phosphorus levels in adenine-induced renal failure rats. A final benefit for regulation of the serum phosphorus levels by Renagel® could be the prevention of the ectopic calcification and ROD in hemodialysis patients.

Adenine-induced renal failure rats have been shown to exhibit hyperphosphatemia according to the severity of chronic renal failure [15, 16]. Administration of an adenine diet in rats resulted in the deposition of 2,8-dihydroxyadenine in the renal tubules, which consequently induced a severe chronic renal failure due to the degeneration of the proximal and distal tubules and interstitial fibrosis [13, 14]. This study demonstrated that, in adenine-induced renal failure rats, elevated levels of serum calcium × phosphorus product could induce an increase in the ectopic calcification of soft tissues, including blood vessels, kidney, and the muscular layer of the stomach. Furthermore, ROD, which was induced by hyperparathyroidism, was observed to have the characteristics of osteitis fibrosa, with bone resorption cavities and increased osteoid.

In this study, the adenine-induced renal failure rats that were fed sevelamer did not develop significant episodes of ectopic calcification of the soft tissues, including those tissues in the thoracic aorta, kidney, and stomach. Hyperphosphatemia is accompanied by elevated levels of serum calcium × phosphorus product, and most studies on myocardial, vascular, and coronary artery calcification among ESRD patients have reported a strong association between calcification and serum phosphorus and/or calcium × phosphorus product levels [18, 19]. Mönckeberg’s medial sclerosis is one example of typical
vascular calcification in ERSD patients, which may have two different pathogenic mechanisms: a degenerative process that leads to apoptosis or necrosis of medial smooth muscle cells, or an osteogenic process that leads to formation of bone-like structures [20]. In hyperphosphatemia, it has recently been reported that phosphate uptake on smooth muscle cells via a sodium-dependent phosphate cotransporter, increases the expression of Cbfa-1, a bone-specific transcription factor, and that subsequent elaboration of a promineralizing matrix containing osteopontin and osteocalcin can contribute to vascular calcification [21]. In adenine-induced renal failure rats, the calcification of the aorta media, composed of smooth muscle cells, is prominent and the vascular calcification of this model has some histopathologic similarity to Mönckeberg’s medial sclerosis in uremic arterial disease. It is assumed that the efficacies of sevelamer in this study are in agreement with those of the vascular calcification study in ESRD patients [12]. In the ESRD patient study, sevelamer was associated with less progression of both coronary artery and aortic calcification compared with calcium salts. In ESRD patients, arterial calcification is strongly associated with arterial stiffening and increased risk for cardiovascular and total mortality [22, 23]. Coronary calcification in the ESRD population is also associated with a history of cardiovascular events [24]. Furthermore, we found that the aortas of adenine-induced renal failure rats were positive for osteopontin and osteocalcin, while the aortas not expressing ectopic calcification by sevelamer administered were negative.
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Fig. 11. Effect of sevelamer on morphometrical parameters of ROD. Fibrosis volume (A), porosity ratio (B), and osteoid volume (C) were significantly elevated in adenine-induced renal failure rats. However, sevelamer significantly suppressed these morphometric parameters representing the features of renal osteodystrophy (ROD). Data are mean ± SE.

#P < 0.05 vs. normal-control group; **P < 0.01; ***P < 0.001 vs. adenine-control group.

for these expressions. These data suggested that hyperphosphatemia induced the osteoblastic differentiations (although the metastatic bone formation was not observed) in the vascular calcification of adenine-induced renal failure rats, while sevelamer suppressed these changes.

As for nephrocalcinosis, calcification of the kidney was observed in tubular epithelial cells and their basement membrane in adenine-induced renal failure rats. The adenine-induced renal failure rats showed an elevated level of serum PTH, possibly due to increased serum phosphorus levels. Along with elevated levels of serum calcium × phosphorus product, the elevated levels of serum PTH also can induce retention of calcium in the renal tubular cells, which may cause the nephrocalcinosis of tubules and the worsening of renal function [25, 26]. Therefore, it is assumed that the effectiveness of sevelamer, in the prevention of nephrocalcinosis, has two mechanisms—one is a direct suppression of serum calcium × phosphorus product levels, and the other is an indirect effect by decreasing serum PTH levels. As for the serum creatinine, the values showed no significant differences among all groups in our experiment, although data from Cozzolino et al [11] showed improvement of renal function by reduced nephrocalcinosis. The reason is because the adenine-induced renal failure models in this experiment condition were extremely severe (serum creatinine was extremely high), and the suppression of nephrocalcinosis was not enough to prevent the progression of renal failure.

This study also demonstrated that the sevelamer-treated groups showed a significant suppression of serum PTH levels, while the adenine-induced renal failure control rats, with secondary hyperparathyroidism, showed a greatly increased elevation of serum PTH levels. Secondary hyperparathyroidism is known to be induced by low levels of serum calcium and 1,25(OH)2D3 in chronic renal failure patients [27, 28]. Besides this pathway, it has been recently demonstrated that serum phosphorus levels increase the synthesis and secretion of PTH in vitro, and in experimental animals; phosphorus also plays an important role in the development of parathyroid cell hyperplasia [29–31]. In this study, extremely elevated levels of serum phosphorus and decreased levels of serum calcium were thought to cause an elevation in the levels of serum PTH, along with increased hyperplasia of the parathyroid glands.
The results of this study indicate that sevelamer significantly prevents ROD that is induced by hyperparathyroidism in adenine-induced renal failure rats. Secondary hyperparathyroidism is known to induce a high turnover bone disease (ROD), characterized by increases in the activation of osteoblasts and osteoclasts with elevated rates of bone formation [6–8], which is responsible for a significant rate of morbidity. In this experiment, adenine-induced renal failure rats show a marked high turnover type of ROD via elevated levels of serum PTH, which histopathologically represents the activation of osteoblasts and osteoclasts, osteitis fibrosa, an increase in bone resorption cavities, a dramatic increase in the production of osteoids in the endosteum, and a decrease in bone marrow cavity. The histopathology of this model is similar to the mixed type of ROD in ESRD patients, which is characterized by an increase in osteitis fibrosa and osteoid. Sevelamer contributes to the prevention of a progression of ROD in adenine-induced renal failure rats, as well as preventing an increase in osteoid, bone resorption cavities, and osteitis fibrosa. Our data indicate that sevelamer could be a useful compound in treating ROD that is caused by secondary hyperparathyroidism.

CONCLUSION
The adenine-induced renal failure rat may provide a model to test therapeutic agents to prevent both ROD and ectopic calcification. The results indicated that sevelamer was effective in suppressing ectopic calcification and ROD in adenine-induced renal failure rats.

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