Sevelamer hydrochloride, a phosphate binder, protects against deterioration of renal function in rats with progressive chronic renal insufficiency

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Abstract

Background. Dietary phosphate restriction prevents renal function deterioration in animal models. This study examined whether sevelamer hydrochloride (Renagel®; ‘sevelamer’ hereafter), a non-calcaemic phosphate binder could slow deterioration of renal function in rats with progressive renal insufficiency.

Methods. Wistar Kyoto male rats were singly injected with normal rabbit serum or rabbit anti-rat glomerular basement membrane serum. Three days later, rats were fed a powder diet containing 0, 1 or 3% sevelamer for 58 days. Time course changes of serum levels of blood urea nitrogen (BUN), creatinine, calcium, phosphorus and parathyroid hormone (PTH) were measured throughout, and creatinine clearance (CCr), kidney calcium content and renal histology examined at the end of the study.

Results. Sevelamer partially inhibited elevation of BUN and serum creatinine, and completely inhibited increases in serum phosphorus, PTH and calcium x phosphorus product. Sevelamer significantly prevented the decrease in CCr and kidney calcium content elevation. Kidney calcium content and BUN and serum creatinine were strongly positively correlated, and kidney calcium content and CCr strongly negatively correlated. Kidney calcium content correlated well with serum phosphorus, serum calcium x phosphorus product and PTH, but not serum calcium. Sevelamer treatment partly prevented histological deterioration of both glomerular and tubulointerstitial lesions of the kidney.

Conclusions. The results suggest that sevelamer protects against renal function deterioration by maintaining kidney calcium at a low level as a result of reducing serum phosphorus and PTH.

Keywords: nephrocalcinosis; parathyroid hormone; phosphate binder; renal function; serum phosphorus; sevelamer hydrochloride (Renagel®)

Introduction

Phosphate is one of many factors that can promote progression of renal failure. There is ample evidence that dietary phosphate overload accelerates, and dietary phosphate restriction prevents, the progression of chronic renal insufficiency (CRI) in experimental animal models [1–6]. Although the mechanism of phosphate toxicity in renal failure has not been fully established, nephrocalcinosis, renal haemodynamics and intrarenal hypermetabolism are considered to be involved [5,6].

Calcium carbonate and acetate have been widely used as phosphate binders in patients with end-stage renal disease. However, there is a limit on the use of these calcium-containing phosphate binders in predialysis patients because of the risk of causing deterioration of renal function by nephrocalcinosis. Sevelamer hydrochloride (Renagel®; hereafter referred to as sevelamer) is a calcium-free and aluminium-free phosphate-binding polymer marketed for the treatment of hyperphosphataemia in patients undergoing haemodialysis. Many beneficial effects of sevelamer have been demonstrated in experimental animals [7,8] and in the clinic [9–11], such as a prevention of parathyroid hyperplasia and lowering of serum phosphorus, calcium x phosphorus product, parathyroid hormone (PTH), and low-density lipoprotein (LDL) cholesterol without increasing serum calcium levels. It is thought

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that the reduction of calcium x phosphorus product and LDL cholesterol levels could reduce the incidence of metastatic calcification. Indeed, long-term studies employing electron beam computed tomography have demonstrated beneficial effects of sevelamer, as compared with calcium-based phosphate binders, on cardiac and aortic calcification in patients receiving haemodialysis [11].

It is known that Wistar Kyoto (WKY) rats are more susceptible to anti-glomerular basement membrane (GBM) serum than other strains. WKY rats injected with a small volume of anti-GBM serum rapidly progress to CRI with glomerulosclerosis and tubulo-interstitial scarring [12]. It has been suggested that macrophages as well as CD8-positive T lymphocytes are involved in the initiation and subsequent progression of CRI in this model [13,14]. Wada et al. [13] have reported that injection of antibody against monocyte chemoattractant protein-1 (MCP-1), a monocyte recruiting and activating factor, prevents glomerulosclerosis and renal dysfunction with inhibition of macrophage infiltration.

In the present study, we examined whether dietary treatment with sevelamer could prevent the progression of CRI in this animal model. In addition, the protective effect of sevelamer on renal function was analysed with particular attention to nephrocalcinosis.

Subjects and methods

Experimental protocol

The experimental protocol was approved by the Experimental Animal Ethical Committee of Kirin Brewery Co., Ltd. Male WKY rats, 8 weeks of age, were purchased from Charles River Japan (Tokyo, Japan) and fed a standard powder diet containing 0.85% phosphorus, 1.12% calcium, 25.3% crude protein and 2.5 IU/g vitamin D3 (CE-2, CLEA Japan, Tokyo, Japan). Rats were kept singly in cages and allowed free access to food and water. After an acclimatization period of 7 days, the WKY rats, 8 weeks of age, SLC Japan). Two weeks after the last subcutaneous (s.c.) immunization, blood was collected from the cervical arteries under pentobarbital sodium anaesthesia.

Preparation of antibody

Rat GBM was prepared from 54 male Sprague–Dawley (SD) rats (10–12 weeks of age, SLC Japan, Tokyo, Japan) by the method of Shibata [15]. GBM was digested with trypsin at 37°C for 3 h. After heating at 60°C for 30 min, the mixture was centrifuged at 27 000 r.p.m. at 3°C for 35 min and the supernatant lyophilized. The lyophilized sample was mixed with complete Freund’s adjuvant (Difco Laboratories, MI, USA) and injected subcutaneously four times at intervals of 1–2 weeks into four male rabbits (New Zealand White, 13 weeks of age, SLC Japan). Two weeks after the last immunization, blood was collected from the cervical arteries under pentobarbital sodium anaesthesia (20 mg/kg, i.v.). Sera were separated and immobilized at 56°C for 30 min and frozen at –80°C until use. Specificity was confirmed by the Ouchterlony gel diffusion method: a clear common precipitate line was observed between antigen and diluted antisera. In addition, anti-GBM antibody gave a strong positive finding of the GBM on frozen sections of normal SD rat kidney when followed by incubation with fluorescein isothiocyanate conjugated anti-rabbit IgG (Seikagaku Kogyo Co., Ltd, Tokyo, Japan).

Kidney calcium content

The right kidneys were frozen at −20°C for subsequent analysis. After lyophilization, dried kidneys were delpidized with a mixed solution of chloroform and methanol (2:1) for 48 h, and dehydrated by acetone for 3 h. Samples were burned to ash at 550°C for 12 h using an electric muffle furnace (KM-600, Advantec Toyo Seisakusho Co., Ltd, Tokyo, Japan), and then dissolved in hydrochloric acid. Before measuring calcium by means of a commercial kit (OCPC method, Wako Pure Chemical Industries, Ltd.), the solution was diluted with an appropriate volume of distilled water.

Histological evaluation

The left kidneys were fixed in Bouin’s fixative, composed of picric acid, formalin and acetic acid, at 4°C overnight. After dehydration by passage through an ethanol/xylene series,
tissues were embedded in TissuePrep (Fisher Scientific Co., NJ, USA) and cut into 1 μm sections. After sequential dewaxing and rehydration, slides were stained with haematoxylin–eosin and periodic acid–Schiff for histological evaluation.

A semi-quantitative scoring procedure was carried out at the Takasaki Pathology Center of Nippon Experimental Medical Research Institute Co. Ltd (Takasaki, Japan) to evaluate the degree of tissue damage. 100 glomeruli in each specimen were examined and the severity of the lesion was graded from 0 to 4+. Thus, a 1+ lesion represented a one-quarter area of the glomerulus revealing sclerosis while a 4+ lesion indicated four-quarters of the area of the glomerulus revealing sclerosis. The injury scores of 100 glomeruli were summed. Tubulointerstitial lesions were similarly scored according to severity. Thus, a 1+ represented a 0–25% mild lesion and a 4+ represented a 75–100% severe lesion.

Drugs
Sevelamer (cross-linked poly[allylamine hydrochloride], the active ingredient of Renagel®) was synthesized by The Dow Chemical Company (Midland, MI, USA) and supplied via Chugai Pharmaceuticals Co., Ltd (Tokyo, Japan).

Statistics
All values are expressed as means ± SEM. The data obtained from control and CRI rats receiving a normal diet were compared using the Student’s t-test. Multiple comparisons were performed among the three CRI groups using the parametric Dunnett’s test. The correlation between kidney calcium content and serum parameters and CCr was analysed using Pearson’s correlation test. P < 0.05 was taken to indicate statistical significance.

Results

Body weight and food intake volume
Body weight was significantly lower in the CRI rats and the difference increased as the study progressed (Figure 1). The body weights in the sevelamer treated groups were larger than those of the CRI rats receiving a normal diet and the differences between the normal diet group and the 3% sevelamer group on day 44 and 51 were statistically significant. Mean food intake volumes (g/day), measured weekly throughout the study, were as follows: control, 18.6 ± 0.2; CRI rats receiving normal diet, 14.0 ± 0.3; 1% sevelamer, 15.3 ± 0.3; 3% sevelamer, 16.5 ± 0.3. The mean administered sevelamer doses (mg/day) throughout the study were calculated as 153.2 ± 2.7 and 496.0 ± 10.2 in the 1 and 3% sevelamer groups, respectively. One animal died at day 45 in the 3% sevelamer group and one animal in the CRI group receiving a normal diet died at day 53.

Serum and urinary chemistries
Hypocalcaemia was observed in the CRI groups from days 3 to 38 and treatment with sevelamer had no obvious effect on serum calcium levels at any time (Figure 2A). Serum phosphorus progressively increased in the CRI rats receiving a normal diet as the study progressed. The 1% sevelamer treatment significantly inhibited the occurrence of hyperphosphataemia, and the 3% sevelamer treatment kept serum phosphorus levels below control levels from days 3 to 38 and then maintained normal levels (Figure 2B). The changes in serum calcium × phosphorus product of all groups

![Fig. 1. Effect of dietary treatment with sevelamer on body weight changes in rats with CRI. Values are mean ± SE (n = 11–12) and the missing SEM bars are hidden within the symbols. Control rats were fed a normal diet (filled circle) and rats with CRI were fed either a normal diet (open circle), or a diet containing 1 (open triangle) or 3% sevelamer (open square) for 58 days. *P < 0.05 vs rats with CRI fed a normal diet. **P < 0.05 vs rats with CRI fed a normal diet. ***P < 0.001 vs control rats fed a normal diet.](image-url)
were similar to the changes in serum phosphorus throughout the study (Figure 2C).

BUN and serum creatinine levels increased gradually from days 3 to 38 and sharply after day 38 in the rats receiving a normal diet while they were within the normal ranges in the control group. One per cent sevelamer treatment appeared to inhibit the elevation of BUN and serum creatinine levels but the differences
were not statistically significant, whereas 3% sevelamer treatment inhibited these increases to a statistically significant extent (Figure 3A and B). Serum PTH rose progressively and steeply parallel to the elevation of BUN and serum creatinine. Both 1 and 3% sevelamer treatments maintained serum PTH levels at control levels until day 52. At the end of the study, a slight elevation was observed in the 1% sevelamer group while there was still no increase in the 3% sevelamer group (Figure 3C).

Serum total cholesterol increased markedly in all three CRI groups. This was not affected by 1% sevelamer, but 3% sevelamer tended to cause a decrease throughout the study (Table 1). A marked reduction in serum 1.25(OH)2D3 levels was observed in CRI rats receiving a normal diet at the end of the study (Table 1). This was unaffected by 1% sevelamer, but 3% sevelamer tended to reverse this effect to an extent, although the level remained much lower than in the controls. A 3.1-fold elevation of serum MCP-1 levels was observed at the end of the study in the CRI rats receiving a normal diet (Table 1). Sevelamer treatment did not affect this increase.

CRI rats receiving a normal diet showed marked polyuria and massive proteinuria at the end of the study (Table 1), and neither 1 nor 3% sevelamer treatment affected these parameters. Significant decreases in urinary calcium, phosphorus and calcium × phosphorus product were observed in CRI rats receiving a normal diet (Table 1). Sevelamer increased urinary calcium concentration and decreased urinary phosphorus concentration in a dose-dependent manner. Urinary calcium × phosphorus product was not significantly affected by the sevelamer treatment.

CCr and kidney calcium content
CCr of the CRI rats receiving a normal diet decreased significantly to 13% of the control group. Treatment with 1% sevelamer tended to increase CCr but not significantly, and 3% sevelamer increased CCr to a significant extent at the end of the study (Figure 4A). The kidney calcium content of the control group was almost the same as that of the baseline group. A 4.8-fold increase in kidney calcium content was observed in the CRI rats receiving a normal diet. The 1 and 3% sevelamer treatments decreased kidney calcium content to 52 and 39%, respectively, of that of the CRI rats receiving a normal diet (Figure 4B).

Correlation analysis
Kidney calcium content was highly correlated with BUN and serum creatinine levels (Figure 5). As expected, we observed a strong negative correlation between kidney calcium content and CCr. Kidney calcium content also correlated well with serum phosphorus, serum calcium × phosphorus product and serum PTH levels (Figure 6). In contrast, no significant correlation was observed between kidney calcium content and serum calcium.

Histology
Each photograph shown in Figure 7 is of the renal cortex of the rat whose serum creatinine level was closest to the mean of each group. Control animals displayed normal renal histology (Figure 7A). In contrast, many kinds of glomerular lesions, such as glomerular hypertrophy, glomerular atrophy, focal segmental sclerosis, crescentic formation and Bowman’s capsule thickening occurred extensively in the kidneys of the CRI rats receiving a normal diet (Figure 7B). Tubulointerstitial changes, such as dilated tubules with decidualation of the brush border membrane, tubular atrophy, infiltration of mononuclear cells, fibrosis and cast formation also dominated in this group. The extent of histological deterioration was almost the same in the CRI group receiving a normal diet and the 1% sevelamer group (data not shown). In contrast, glomerular sclerosis and tubulointerstitial lesions tended to be reduced in the 3% sevelamer group (Table 2) although some degree of crescentic formation and thickening of Bowman’s capsule still remained (Figure 7C). Markedly increased mononuclear cell infiltration in the periglomerular and tubulointerstitial regions was observed in the CRI animals receiving a normal diet. Sevelamer treatment did not significantly affect the number of mononuclear cells in the tubulo-interstitial regions (Table 2).

Discussion
Sevelamer treatment increased both food intake volume and body weight gain in the CRI rats. It is likely that this effect is due, in part, to an improvement in renal function. Hence, although it is widely accepted that dietary protein restriction as well as phosphate restriction can protect against deterioration of renal function in experimental animal models, we can clearly exclude the effect of dietary protein intake from the renal protective effect of sevelamer in this study.

Sevelamer treatment clearly inhibited the elevation of BUN and serum creatinine levels and prevented the reduction of CCr in rats with CRI. This protective effect of sevelamer on renal function was supported by histological observations showing that both glomerular sclerosis and tubulointerstitial lesions were partially ameliorated. In a previous experiment using CRI rats induced by adriamycin (ADR), we observed that sevelamer treatment tended to inhibit the elevation of BUN and to prevent the reduction of CCr, but the effects were not statistically significant [8]. A possible explanation for the lack of a clear cut renal protective effect of sevelamer in that case may be the 4-week delay that ensued between the initiation of renal injury and the start of sevelamer treatment. Irreversible changes had probably already taken place during this interval because the ADR rats showed marked proteinuria and hypercholesterolaemia at the onset of sevelamer treatment. Despite the outcome of studies with experimental animals, phosphate restriction is not an established
approach for delaying the progression of renal failure in the clinic. However, a beneficial effect of dietary phosphate restriction has been reported in patients with an early stage of CRI [6]. A similar explanation to that given above might apply, namely that the phosphate-restricted regimens were started long after the onset of CRI.

Although many mechanisms for the protective effect of sevelamer need to be examined, the present study suggests that the primary mechanism is the prevention
of nephrocalcinosis. Sevelamer maintained serum phosphorus at a low level and prevented nephrocalcinosis. In experimental studies, removal of phosphate from the medium of cultured monkey kidney cells reduced intracellular calcium content both by reducing calcium influx and increasing efflux [16]. It is widely accepted that increased intracellular calcium induces cell death, fibrosis and scarring. Therefore, the protective effect of sevelamer on renal function is perhaps achieved by preventing nephrocalcinosis owing to the lower concentration of extracellular phosphorus. Serum calcium/\textsuperscript{2} phosphorus product has been used as a reliable parameter for predicting metastatic calcification. We have directly demonstrated above that reduction of this parameter by sevelamer is strongly associated with inhibition of nephrocalcinosis. In contrast to serum, a pronounced decrease in urinary calcium/\textsuperscript{2} phosphorus product associated with polyuria was observed in CRI rats receiving a normal diet. Although it has been suggested that increased tubular fluid phosphorus and calcium/\textsuperscript{2} phosphorus product results in tubular calcium-phosphate precipitation [5], this is not likely to be one of the causes of nephrocalcinosis in this experimental model. Sevelamer treatment increased urinary calcium and decreased urinary phosphorus concentrations, and we have observed that in normal rats these effects of sevelamer are mainly mediated by a reduction of serum PTH [7]. It is interesting to note that PTH-regulated mechanisms for renal mineral handling are preserved in rats with severe CRI.

Sevelamer treatment markedly inhibited the elevation of serum PTH, and there was a strong positive correlation between serum PTH and kidney calcium content. The decrease in serum PTH achieved by sevelamer treatment is probably mainly due to prevention of hyperphosphataemia and partly due to the preservation of renal function. PTH has been considered an important cause of nephrocalcinosis because administration of parathyroid extract results in renal calcification [17,18] by increasing cytosolic calcium in proximal tubular cells [19,20].

### Table 1. Effect of dietary treatment with sevelamer on serum and urinary chemistries

<table>
<thead>
<tr>
<th>Group</th>
<th>Control + normal diet</th>
<th>CRI + normal diet</th>
<th>CRI + 1% sevelamer</th>
<th>CRI + 3% sevelamer</th>
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<tbody>
<tr>
<td>No. of animals</td>
<td>12</td>
<td>11 or 12</td>
<td>12</td>
<td>11 or 12</td>
</tr>
<tr>
<td>Serum chemistries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>96.9 ± 1.9</td>
<td>291 ± 10###</td>
<td>262 ± 9</td>
<td>237 ± 16**</td>
</tr>
<tr>
<td>(Day 17)</td>
<td>102 ± 2</td>
<td>410 ± 9###</td>
<td>398 ± 11</td>
<td>354 ± 29</td>
</tr>
<tr>
<td>(Day 38)</td>
<td>97.9 ± 2.1</td>
<td>326 ± 29###</td>
<td>326 ± 23</td>
<td>307 ± 21</td>
</tr>
<tr>
<td>1,25(OH)\textsubscript{2}D\textsubscript{3} (pg/ml)</td>
<td>32.4 ± 1.7</td>
<td>2.9 ± 0.8###</td>
<td>3.1 ± 0.6</td>
<td>5.3 ± 1.5</td>
</tr>
<tr>
<td>MCP-1 (pg/ml)</td>
<td>723 ± 130</td>
<td>2256 ± 25###</td>
<td>2317 ± 144</td>
<td>1985 ± 400</td>
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<tr>
<td>Urinary chemistries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (ml/day)</td>
<td>18.4 ± 1.1</td>
<td>36.7 ± 2.7###</td>
<td>39.8 ± 1.9</td>
<td>33.6 ± 4.1</td>
</tr>
<tr>
<td>Protein (mg/kg, b.w.)</td>
<td>53 ± 3.5</td>
<td>1263 ± 97###</td>
<td>1222 ± 66</td>
<td>1011 ± 80</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>10.5 ± 1</td>
<td>3.4 ± 0.4###</td>
<td>5.5 ± 0.4</td>
<td>13.8 ± 3.2***</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>147 ± 8</td>
<td>55.2 ± 2.1###</td>
<td>31.4 ± 1.5**</td>
<td>19.7 ± 3.7***</td>
</tr>
<tr>
<td>Calcium × phosphorus (mg\textsuperscript{2}/dl\textsuperscript{2})</td>
<td>1549 ± 182</td>
<td>186 ± 23###</td>
<td>177 ± 21</td>
<td>317 ± 140</td>
</tr>
</tbody>
</table>

All parameters except serum cholesterol were determined at the end of the study. ***P < 0.001 vs control rats fed a normal diet. **P < 0.01, ***P < 0.001 vs rats with CRI fed a normal diet.

Fig. 4. Effect of dietary treatment with sevelamer on CCr (A) at the end of the study and kidney calcium content (B) at baseline and at the end of the study in rats with CRI. Values are mean ± SE \((n=11–12)\) and the missing SEM bars are hidden within the columns. ###P < 0.01, ####P < 0.001 vs control rats fed a normal diet. *P < 0.05, **P < 0.01 vs rats with CRI fed a normal diet.
Phosphate binder protects renal function

Fig. 5. Analysis of the correlations between BUN (A), serum creatinine (B) and CCr (C) with kidney calcium content in the baseline group (open diamond), control rats fed a normal diet (filled circle), and rats with CRI fed either a normal diet (open circle), or a diet containing 1% (open triangle) or 3% sevelamer (open square) for 58 days.

Fig. 6. Analysis of the correlations between levels of serum calcium (A), phosphorus (B), calcium \times phosphorus product (C) and PTH (D) with kidney calcium content in the baseline group (open diamond), control rats fed a normal diet (filled circle), and rats with CRI fed either a normal diet (open circle), or a diet containing 1% (open triangle) or 3% sevelamer (open square) for 58 days.
parathyroidectomy can prevent renal calcification and functional deterioration [21]. In addition, the PTH-induced increase in intracellular calcium in kidney cells is greatly enhanced by the presence of phosphate in the extracellular medium [20]. It is therefore possible that the reduction in serum phosphorus and the reduction in PTH levels brought about by sevelamer treatment act synergistically to reduce nephrocalcinosis.

Another explanation is also possible. The reduction in serum phosphorus and PTH levels due to sevelamer treatment may alter local immunological and inflammatory processes in the kidney and this may help preserve renal function. Marked elevation of serum MCP-1 levels and increased infiltrated mononuclear cell number were observed in rats with CRI. Macrophages are considered to play an important role in pathogenesis in this model, especially in glomerular crescent formation [13,14]. However, there were no obvious differences in serum MCP-1 levels and in the number of infiltrated mononuclear cells between the normal diet group and the 3% sevelamer group in the rats with CRI. Macrophages are also known to play an important role in arterial intimal calcification [22]. Nonetheless, there did not seem to be any relationship between nephrocalcinosis and mononuclear cell accumulation in the present study. Sevelamer decreased nephrocalcinosis without affecting mononuclear cell infiltration. It has been reported that dietary phosphate restriction reduces proteinuria in the remnant kidney model [2,4] but not in the immuno-mediated glomerulonephritis model [3]. The latter finding is supported by our failure to observe any obvious protective effect of sevelamer on urinary protein excretion, crescent formation or Bowman’s capsule thickening. Thus, it is unlikely that immunological and inflammatory processes mediate the protective effect of sevelamer on renal function.

Another beneficial action of sevelamer is a reduction in LDL cholesterol in patients receiving hemodialysis, because this should reduce the probability of cardiovascular disease and possibly prolong survival [9–11]. Many studies on experimental animal models have demonstrated that lipid abnormalities aggravate renal injury in many forms of atherosclerosis [23]. In particular, activated macrophages are thought to play an important role in the etiology of renal injury and atherosclerosis when lipid levels are perturbed. In this study, a marked increase in serum total cholesterol was

![Fig. 7.](image)

**Table 2.** Histological evaluation of glomerular and tubulointerstitial lesions by semi-quantitative scoring

<table>
<thead>
<tr>
<th>Group</th>
<th>Control + normal diet</th>
<th>CRI + normal diet</th>
<th>CRI 1% sevelamer</th>
<th>CRI + 3% sevelamer</th>
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<td>No. of animals</td>
<td>12</td>
<td>11</td>
<td>12</td>
<td>11</td>
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<tr>
<td>Glomerular lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular sclerosis</td>
<td>0</td>
<td>226 ± 18</td>
<td>225 ± 16</td>
<td>152 ± 18*</td>
</tr>
<tr>
<td>Tubulointerstitial lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0</td>
<td>1.55 ± 0.21</td>
<td>1.75 ± 0.18</td>
<td>1.09 ± 0.09</td>
</tr>
<tr>
<td>Mononuclear cell infiltration</td>
<td>0</td>
<td>1.55 ± 0.21</td>
<td>1.75 ± 0.18</td>
<td>1.09 ± 0.09</td>
</tr>
<tr>
<td>Protein cast</td>
<td>0</td>
<td>2.91 ± 0.09</td>
<td>2.08 ± 0.23*</td>
<td>2.27 ± 0.27</td>
</tr>
<tr>
<td>Dilated tubule</td>
<td>0</td>
<td>2.82 ± 0.18</td>
<td>2.58 ± 0.15</td>
<td>2.55 ± 0.21</td>
</tr>
</tbody>
</table>

*P < 0.05 vs rats with CRI fed a normal diet.
observed in rats with CRI and sevelamer treatment tended to counteract this effect. To determine whether a part of the renal protective effect of sevelamer derives from its cholesterol-lowering action, it will be necessary to measure serum LDL cholesterol levels and compare the effect of a low phosphorus diet or aluminum-containing diet that serum phosphorus levels are comparable with those in the 3% sevelamer group.

It is well known that 1,25(OH)2D3 is a potent cause of nephrocalcinosis. In the present study, we observed a marked reduction in serum 1,25(OH)2D3 in CRI rats. Although 1% sevelamer had no effect, 3% sevelamer tended to increase 1,25(OH)2D3 levels, although they remained much lower than in the controls. The slight increase in 1,25(OH)2D3 produced by 3% sevelamer might in part brought about by preventing the deterioration of proximal tubules. In any event, these results demonstrate that the protective effect of sevelamer on renal function is independent of renal 1,25(OH)2D3 production.

In conclusion, sevelamer protected against deterioration of renal function, maintaining a low level of kidney calcium content by reducing serum phosphorus and PTH in rats with progressive CRI. This mechanism should be confirmed by additional control studies with alternative phosphate binders, cholesterol-lowering agents, dietary phosphate restriction or parathyroidectomy.

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Conflict of interest statement. N.N., S.M., S.O., N.K. and M.W. are employees of Kirin Brewery Co., Ltd. N.F. is an employee of Chugai Pharmaceuticals, Inc. S.K.B. is an employee of GelTex Pharmaceuticals, Inc. GelTex, Chugai and Kirin are developers of sevelamer hydrochloride.

References


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