Sevelamer Decreases Serum Uric Acid Concentration through Adsorption of Uric Acid in Maintenance Hemodialysis Patients

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Abstract

Background Sevelamer, a nonabsorbed hydrogel that binds phosphate, is reported to reduce the serum urate concentration in maintenance hemodialysis patients, however the urate-lowering mechanism remains obscure. In this study we verify the urate-lowering effect of sevelamer in Japan in which the hemodialysis environment is different from that of western countries, and we also clarify the urate-lowering mechanism of sevelamer.

Methods A total of 127 Japanese patients undergoing maintenance hemodialysis were investigated. These patients consisted of 93 males and 34 females, and their mean age was 58.4±12.4 years (range, 25-88 years). The mean duration of hemodialysis was 8.7±6.1 years (range, 0.5-27.5 years). Sevelamer was added to each patient’s former prescription for the treatment of hyperphosphatemia, and the changes in laboratory data before and after administration of sevelamer were compared. In order to clarify the mechanism of urate-lowering effect by sevelamer, a urate adsorption experiment was carried out in vitro.

Results Sevelamer significantly decreased serum phosphate value three and six months after administration. Sevelamer showed a significant reduction in serum urate values in maintenance hemodialysis patients with hyperuricemia, but not in patients with normouricemia. The change rate of serum urate correlated with the change rate of serum phosphate and the change rate of serum calcium × phosphate product, but did not correlate with that of serum calcium. Sevelamer hydrochloride adsorbed urate in vitro.

Conclusion Sevelamer decreases serum urate possibly by adsorbing urate in hemodialysis patients.

Key words: AST-120, hemodialysis, hyperphosphatemia, hyperuricemia, sevelamer

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Introduction

Hyperphosphatemia is one of the most important risk factors for cardiovascular disease and death in maintenance hemodialysis patients (1, 2). Accordingly, the measures for treating hyperphosphatemia in these patients are very important. Dietary phosphate restriction and phosphate binders are usually employed for this purpose. Aluminium hydroxide which has a strong phosphate-binding capacity was used as a phosphate binder in the past. However aluminium hydroxide is now contraindicated because the absorbed aluminium causes various severe diseases like aluminium-induced bone disease, encephalopathy, and anemia. Presently, precipitated calcium carbonate and sevelamer, a nonabsorbed hydrogel that binds phosphate, are used for the purpose of lowering serum phosphate (3, 4).

Because most uric acid is excreted from the kidney, hyperuricemia is usually seen in renal insufficiency patients and maintenance hemodialysis patients. Allopurinol, a xanthine oxidase inhibitor, is used for the treatment of hyperuricemia in patients with reduced GFR. Allopurinol can gen-
naturally be used safely in chronic kidney disease, although dose adjustments are required due to impaired clearance of oxypurinol, the major active metabolite of allopurinol (5). Consequently, there is insufficient control of hyperuricemia in renal failure patients. There is a need for a uric acid-lowering medicine that can be used safely even in renal failure.

Garg et al reported that sevelamer reduces serum uric acid concentration in maintenance hemodialysis patients (6), however the uric acid-lowering mechanism remains unknown. In the present study, we verified the uric acid-lowering effect of sevelamer in Japan in which the hemodialysis environment is different from that in western countries, and we also clarified the uric acid-lowering mechanism of sevelamer.

**Subjects and Methods**

**Study 1: Clinical study**

A total of 127 Japanese patients undergoing maintenance hemodialysis were investigated. These patients consisted of 93 males and 34 females, and their mean age was 58.4±12.4 years (range, 25-88 years). The mean duration of hemodialysis was 8.7±6.1 years (range, 0.5-27.5 years). The original renal diseases were chronic glomerulonephritis in 47 patients (37.0%), diabetic nephropathy in 33 patients (26.0%), nephrosclerosis in 5 patients (3.9%), polycystic kidney disease in 5 patients (3.9%), gouty kidney in 3 patients (2.4%), and unknown renal disease in 34 patients (26.8%). The rates of these diseases were relatively similar to those in the general Japanese population undergoing maintenance dialysis (7). Informed consent was obtained from all patients.

For these patients, sevelamer was added to each patient’s former prescription for the treatment of hyperphosphatemia, and the changes in laboratory data before and after the administration of sevelamer were compared. The prescription of each patient was not changed except for sevelamer. The dose of sevelamer was 2.5±1.9 (0.5-7.5) g/day at 0 month, 2.7±1.8 (0.5-7.5) g/day at 3 months, and 3.0±1.8 (0.75-8.5) g/day at 6 months. Medicines, which may affect the urate metabolism, such as diuretics and allopurinol, were not changed during the observation period.

**Study 2: In vitro study**

The urate adsorption experiment was carried out as follows: 16 mL of urate solution (200 or 2,000 μg in 4 mM-sodium phosphate buffer, pH8.0) and 4 mL of sevelamer hydrochloride or AST-120, an oral adsorbent medicine (as a positive control), solution (50 or 250 mg in 4 mM-sodium phosphate buffer, pH8.0) was mixed and incubated in 50 mL of a conical tube (BD Falcon™) at 37°C and 150 rpm for 60 minutes. After centrifugation at 3,000 rpm for 5 minutes, the supernatant passing through a milipore filter (pore diameter: 0.45 μm) was assayed for urate concentration by the HPLC method. All assays were performed in triplicate. HPLC was performed under the following conditions: Column: ODS(C18) 4.6×250 mm, Eluent: 4 mM-sodium phosphate buffer, pH 8.0, Flow rate: 1.0 mL/min, Retention time: 3.658-3.706 min, at 254 nm, Pressure: 80-90 kgf/cm². R² for the calibration curve of urate in this assay was 0.9999999988, therefore, this HPLC method was adequately reliable.

**Statistical analysis**

Group differences were assessed by the Mann-Whitney U test and Scheffe’s F test with ANOVA. Correlation between two variables was assessed by Spearman’s rank correlation test. All analyses were performed with the “StatView for Windows version 5.0” software program. All data are shown as mean±SD. p<0.05 was considered statistically significant in all the analyses.

**Results**

**Study 1**

Sevelamer significantly decreased serum phosphate values three and six months after administration. Serum phosphate values were 6.46±1.51 mg/dL (0M, pre), 5.89±1.30 mg/dL (3M), and 6.01±1.18 mg/dL (6M); (0M vs 3M: p=0.0007, 0 M vs 6M: p=0.0224). There was a significant negative correlation between serum phosphate value (pre) and the change rate of serum phosphate (3M: r=-0.513, p<0.0001; 6 M: r=-0.627, p<0.0001).

There was a significant negative correlation between the serum urate value (pre) and the change rate of serum urate (3M: r=-0.337, p<0.0001; 6M: r=-0.285, p=0.0018). Figure 1 shows the correlation between serum urate before sevelamer treatment and the change rate of serum urate 6 months after sevelamer treatment. However there was no correlation between the dose of sevelamer and the change rate of both serum phosphate and urate.

As shown in Fig. 2, sevelamer decreased serum urate value in patients with hyperuricemia (serum urate>7.0 mg/dL) at the start of treatment. Serum urate value were 8.40±1.06 mg/dL (0M, pre), 8.03±1.44 mg/dL (3M), and 7.96±1.61 mg/dL (6M); (0M vs 3M: p=0.0355, 0 M vs 6M: p=0.0152). On the contrary, sevelamer did not affect serum urate values in patients with normouricemia (serum urate≤7.0 mg/dL) at the start of treatment. Serum urate values were 6.42±0.48 mg/dL (pre), 6.57±0.76 mg/dL (3M), 6.56±0.87 mg/dL (6M).

As shown in Fig. 3, there were significant positive correlations between the change rate of urate and both the change rate of phosphate (6M, r=0.214, p=0.0207) and the change rate of calcium × phosphate product (6M, r=0.202, p=0.0277), however no correlation was found between the change rate of urate and the change rate of calcium (6M). Serum intact PTH value was significantly correlated with the serum urate and phosphate value (3M: r=0.283, p=0.018).
0.0119, 6M: r=0.354, p=0.0017 between PTH and urate; 3M: r=0.259, p=0.0219, 6M: r=0.239, p=0.0390 between PTH and phosphate. The change rate of urate did not depend on the usage of furosemide, the usage of allopurinol, alcohol drinking, and gender difference (data not shown).

Study 2

In order to clarify the mechanism of the urate lowering effect of sevelamer hydrochloride, an adsorption experiment to determine whether this adsorbent can adsorb the urate in vitro was carried out and AST-120, an oral adsorbent agent, was used as a positive control. Two doses of urate (200 μg or 2,000 μg/tube) were applied to the adsorbents. The results are shown in Fig. 4.

Experiment 1: 200 μg of urate per tube was applied to the adsorbents (left panel of Fig. 4). The urate was adsorbed 72.1±0.7% by 50 mg of sevelamer hydrochloride and 99.1±0% by 50 mg of AST-120. In contrast, the urate was adsorbed 95.1±0% by 250 mg of sevelamer hydrochloride and 100±0% by 250 mg of AST-120.

Experiment 2: 2,000 μg of urate per tube was applied to the adsorbents (right panel of Fig. 4). The urate was adsorbed 69.8±0.6% by 50 mg of sevelamer hydrochloride and 87.2±0.1% by 50 mg of AST-120. However, the urate was adsorbed 95.4±0% by 250 mg of sevelamer hydrochloride and 99.9±0% by 250 mg of AST-120. These results clearly showed that sevelamer hydrochloride adsorbed urate in vitro.

Discussion

From the results of large-scale clinical studies, hyperuricemia seems to be one of the risk factors for cardiovascular disease especially in hypertensive patients (8-10).
Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study, it was found that nearly one-third of the protective effect of losartan against cardiovascular disease is derived from the urate-lowering effect of losartan (11). An
anti-hyperuricemia measure becomes important in renal insufficiency patients accompanied by hypertension. Siu et al. reported that the hyperuricemia treatment by allopurinol restrained a rise in the serum creatinine value in chronic kidney disease patients (12). It is clinically important to find a drug candidate in addition to allopurinol that has a uric acid lowering effect, because the use of allopurinol is limited in patients with renal failure. It might be possible to use febuxostat which is a liver excretion type of xanthine oxidase inhibitor, in the future (13). In dialysis patients, the simultaneous correction of hyperphosphatemia and hyperuricemia, which are thought to be risk factors for cardiovascular diseases, is important. Clinical usefulness is high if it is proved that sevelamer has the dual action of lowering serum phosphate and the urate value.

In Japan, the timing of blood sampling is carried out 3 days after the last dialysis, however in Western countries it is done 2 or 3 days after the last dialysis. Yokoyama et al. reported that serum phosphate levels measured on Monday or Tuesday were significantly higher than those measured midweek (14). From this point, he indicated that the universal guidelines for the management of ROD by K/DOQI should specify the timing of blood collection. Because of this kind of difference in the dialysis environment between Japan and Western countries, it is not clear whether or not the results of Garg et al. concerning the urate lowering effect of sevelamer (6) are relevant to Japan. Our results support the data reported by Garg et al. as applied to Japanese dialysis patients. Because there are no changes in BUN levels before and after sevelamer treatment (6M, -3M, 0M, 3M, 6M, data not shown), the cause of serum urate reduction is not thought to be a change in dialysis efficiency, but rather an effect of sevelamer. The fact that the change in urate correlated with the change in phosphate and the change in calcium × phosphate product (Fig. 3) supports the suggestion that the urate-lowering effect of sevelamer is the result of direct urate adsorption by sevelamer, similar to the phosphate-lowering effect of sevelamer.

Serum urate values were significantly correlated with serum intact PTH values in this study. This suggests that the urate-lowering effect of sevelamer might be derived from a reduced PTH value, because hyperparathyroidism can also promote hyperuricemia via enhanced urate absorption (15). However, there were no differences in the intact PTH values before and after sevelamer treatment (data not shown), so it is unlikely that the change in PTH contributes to the decrease in serum urate values by sevelamer treatment. Meta-analysis of dialysis patients revealed that sevelamer leads to a significant decrease in total cholesterol, LDL cholesterol, triglyceride and a significant increase in HDL cholesterol, in addition to significant decreases in serum phosphate, calcium × phosphate product, and intact PTH (16). The urate-lowering effect of sevelamer might be one more mechanism contributing to the inhibition of cardiovascular disease in dialysis patients.

In study 2, AST-120 was used as the positive adsorbent control. AST-120 is an oral adsorbent engineered to have a large surface area and uniform adsorbing capacity for various low-molecular weight substances including methylguanidine, octopamine, dimethylamine, indole, tryptophan, and indoxyl sulfate (17). Large-scale multicenter double-blind clinical trials have shown that AST-120 delays the initiation of dialysis in patients with chronic renal failure (18, 19). Because enteric excretion of urate is reported to be enhanced in chronic renal failure (20), the urate-adsorbing effect of sevelamer in the gastrointestinal tract might be a reasonable measure in dialysis patients.

The sample size in this study is relatively small, therefore studies using a large number of patients should be conducted in the future to further confirm the urate-lowering effect of sevelamer.

**Conclusion**

Sevelamer, an oral phosphate adsorbent, showed a significant reduction in serum urate values in maintenance hemodialysis patients with hyperuricemia. The mechanism of the urate lowering effect by sevelamer is thought to be enteric urate adsorption, because the change in urate was correlated with a change in phosphate and in calcium × phosphate product, and sevelamer significantly adsorbed urate in vitro. This suggests that sevelamer can serve as a useful urate-lowering medicine in hemodialysis patients.

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**References**


