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Effects of Sevelamer and Calcium-Based Phosphate Binders on Uric Acid Concentrations in Patients Undergoing Hemodialysis

A Randomized Clinical Trial

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Objective. **Gout affects a large fraction of persons with advanced chronic kidney disease, and hyperuricemia may increase the risk of cardiovascular disease. Several hypouricemic agents are contraindicated in patients with end-stage renal disease. Sevelamer is a nonabsorbed hydrogel that binds phosphorus and bile acids in the intestinal tract. Results of short-term and open-label studies suggest that sevelamer might lower the concentration of uric acid, another organic anion. We undertook this study to test our hypothesis that the reduction in serum uric acid concentration induced by sevelamer would be confirmed in a long-term, randomized, clinical trial comparing sevelamer with calcium-based phosphate binders.**

Methods. **Two hundred subjects undergoing maintenance hemodialysis were randomly assigned to receive either sevelamer or calcium-based phosphorus binders in an international, multicenter, clinical trial. Data on baseline and end-of-study uric acid concentrations were available in 169 subjects (85%); the change in uric acid concentration from baseline to the end of the study was the outcome of interest.**

Results. **Baseline clinical characteristics, including mean uric acid concentrations, were similar in subjects randomly assigned to receive sevelamer and calcium-based phosphate binders. The mean change in uric acid concentration (from baseline to the end of the study) was significantly larger in sevelamer-treated subjects (−0.64 mg/dl versus −0.26 mg/dl; $P = 0.03$). The adjusted mean change in uric acid concentration was more pronounced when the effects of age, sex, diabetes, vintage (time since initiation of dialysis), dialysis dose, and changes in blood urea nitrogen and bicarbonate concentrations were considered (−0.72 mg/dl versus −0.15 mg/dl; $P = 0.001$). Twenty-three percent of sevelamer-treated subjects experienced a study-related reduction in the concentration of uric acid equal to −1.5 mg/dl or more, compared with 10% of calcium-treated subjects ($P = 0.02$).**

Conclusion. **In a randomized clinical trial comparing sevelamer and calcium-based phosphate binders, treatment with sevelamer was associated with a significant reduction in serum uric acid concentrations.**

Currently, more than 300,000 persons are undergoing dialysis in the US (1). Persons with chronic kidney disease, including end-stage renal disease (ESRD), experience an increased prevalence of metabolic abnormalities, including hyperphosphatemia, hyperparathyroidism, and hyperuricemia, the last generally defined as a serum uric acid concentration >6.5 or 7.0 mg/dl in men and >6.0 mg/dl in women. Hyperuricemia is largely caused by a reduction in glomerular filtration rate

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(GFR) and, to a lesser extent, by altered uric acid handling associated with certain medications (e.g., diuretic agents). In addition to well-known complications of gout, including inflammatory arthritis and cutaneous tophi, hyperuricemia has been associated with insulin resistance, dyslipidemia, hypertension (metabolic syndrome), and cardiovascular disease. Based on observations from uncontrolled studies (2), we hypothesized that the reduction in serum uric acid concentration induced by sevelamer, a nonabsorbed hydrogel that binds phosphorus, would be confirmed in a long-term, randomized, clinical trial comparing sevelamer with calcium-based phosphate binders.

PATIENTS AND METHODS

Patients. Subjects were adult patients (age ≥19 years) undergoing maintenance hemodialysis who were enrolled at 15 participating dialysis units (7 in the US, 7 in Germany, and 1 in Austria). Exclusion criteria included serious gastrointestinal disease (including dysphagia, active untreated gastroparesis, severe motility disorder, major intestinal surgery, markedly irregular bowel function), ethanol or drug dependence or abuse, active malignancy, human immunodeficiency virus infection, vasculitis, or very poorly controlled diabetes mellitus or hypertension (as deemed by the investigator). Written informed consent was obtained from all subjects. The study was conducted in compliance with the Declaration of Helsinki and the Committees on Human Research at each of the participating universities and dialysis units.

Study design and procedures. *Washout (run-in) phase.* After screening, subjects underwent a 2-week washout period in which all phosphate binders were withheld (weeks −2 to 0). Subjects who developed hyperphosphatemia (serum phosphorus concentrations >5.5 mg/dl) during the washout period were eligible for randomization.

Randomization. Subjects were randomly assigned by computer in a 1:1 ratio to receive either sevelamer or calcium. Subjects were stratified by clinical site and the diagnosis of diabetes mellitus at screening.

Treatment phase. Subjects were randomly assigned to receive sevelamer (Renagel 800-mg tablets; GelTex Pharmaceuticals, Waltham, MA) or calcium-based binders. Subjects randomly assigned to receive calcium in the US received calcium acetate (PhosLo 667-mg tablets; Braintree Pharmaceuticals, Braintree, MA). Those randomly assigned to receive calcium in Europe received calcium carbonate (Sertuerner 500-mg tablets; Sertuerner Arzneimittel, Guetersloh, Germany). Due to the size, appearance, and taste of the tablets, neither the subjects nor the investigators were blinded. Adherence to treatment was estimated by pill counts.

The treatment phase lasted 52 weeks. During the first 12 weeks, the dose of phosphate binder was titrated every 3 weeks to achieve serum phosphorus and calcium concentrations in the target ranges of 3.0–5.0 mg/dl and 8.5–10.5 mg/dl, respectively, and parathyroid hormone (PTH) concentrations in the range of 150–300 pg/ml. After 12 weeks, the doses of phosphate binder and vitamin D and the dialysate calcium concentration could be titrated every 4 weeks to achieve serum phosphorus, calcium, and PTH concentrations in the aforementioned target ranges. Serum uric acid was measured at baseline, 12 weeks, 24 weeks, and 52 weeks. Blood samples were drawn in the middle of the week before dialysis (on Wednesday for subjects undergoing dialysis on Monday, Wednesday, and Friday; on Thursday for subjects undergoing dialysis on Tuesday, Thursday, and Saturday) and analyzed at Quest Diagnostics (Van Nuys, CA, and Heston, Middlesex, UK).

Statistical analysis. Continuous variables were expressed as the mean ± SD or as the median and interquartile range. Between-group comparisons were made with Student's *t*-test or Wilcoxon's rank sum test, as appropriate. Categorical variables were expressed as proportions and compared using Fisher's exact test. Multivariable analyses were performed using least squares regression and were adjusted for the effects of age, sex, vintage (time since initiation of dialysis), diabetes, urea reduction ratio (a parameter of dialysis efficiency), and changes in blood urea nitrogen (BUN) and bicarbonate (proxies for dietary protein intake). For subjects who did not complete 52 weeks of treatment, the last-value-carried-forward method was used. Two-tailed P values less than 0.05 were considered significant. Analyses were conducted using SAS, version 8.02 (SAS Institute, Cary, NC).

RESULTS

Overview. Primary study results have been reported previously (3). Briefly, 200 subjects undergoing maintenance dialysis were randomly assigned to receive either sevelamer or calcium-based phosphorus binders in an international, multicenter clinical trial. Good control of hyperphosphatemia was achieved in both groups. Subjects who received calcium-based binders had significantly higher serum calcium concentrations, were more likely to develop hypercalcemia, and had lower time-averaged PTH concentrations, despite efforts to avoid suppression of PTH below 150 pg/ml. Relative to sevelamer-treated subjects, calcium-treated subjects experienced progressive coronary artery and aortic calcification. There were no significant differences in parameters of mineral metabolism or progression of vascular calcification either by region (US versus Europe) or by the corresponding calcium-based binder used (acetate versus carbonate). The mean ± SD daily dose of sevelamer was 6.5 ± 2.9 gm (corresponding to approximately eight 800-mg tablets per day). Compliance was 86% in sevelamer-treated subjects and 80% in calcium-treated subjects.

Baseline characteristics and uric acid concentrations. Baseline clinical characteristics, including mean uric acid concentrations, were similar in subjects randomly assigned to receive sevelamer and those assigned to receive calcium-based phosphate binders (Table 1).

At baseline, uric acid concentrations were directly correlated with baseline BUN (r = 0.41, $P < 0.0001$), serum creatinine (r = 0.29, $P = 0.0002$), and phosphorus (r = 0.23, $P = 0.003$) levels, and were inversely correlated with age (r = −0.27, $P = 0.0004$), bicarbonate levels (r = −0.19, $P = 0.01$), and the urea reduction ratio (r = −0.15, $P = 0.047$). Baseline uric acid concentrations were higher in men than in women (mean ± SD 6.4 ± 1.3 mg/dl versus 6.0 ± 1.0 mg/dl; $P = 0.025$). There were no significant differences in baseline uric acid concentrations by race or diabetes status.

Changes in concentrations of uric acid and other biochemical markers. At the end of the 52 weeks or at last followup in subjects who did not complete the full 52-week treatment period, the mean (unadjusted) change in uric acid concentration was significantly larger in sevelamer-treated subjects (−0.64 mg/dl versus −0.26 mg/dl; $P = 0.03$). Calcium-treated subjects had significantly larger mean changes in levels of serum calcium (0.43 mg/dl versus −0.01 mg/dl; $P < 0.0001$) and bicarbonate (3.2 mg/dl versus −0.05 mg/dl; $P < 0.001$). Serum phosphorus levels declined in both groups (−2.3 mg/dl versus −2.1 mg/dl in sevelamer- and calcium-treated groups, respectively; $P = 0.42$). There were no significant differences in the change in BUN ($P = 0.93$) or creatinine ($P = 0.32$) levels by binder assignment.

Table 1. Baseline clinical characteristics of the study subjects in whom both baseline and followup data were available*

	Treatment group		
	Sevelamer (n = 81)	Calcium (n = 88)	*P*
Age, years	56 ± 14.0	57.3 ± 15.1	0.70
Women, no. (%)	27 (33)	29 (33)	0.96
African American, no. (%)	16 (20)	19 (22)	0.77
Diabetes, no. (%)	26 (32)	30 (34)	0.78
Vintage, median (IQR) months	43 (20–75)	35 (15–56)	0.16
Previous phosphate binder use, no. (%)			0.66
Calcium acetate	33 (41)	38 (43)	
Calcium carbonate	28 (35)	34 (39)	
Aluminum	5 (6)	1 (1)	
Sevelamer	3 (4)	1 (1)	
Other or combination	12 (15)	14 (16)	
Vitamin D use, no. (%)	42 (52)	54 (61)	0.21
Systolic blood pressure, mm Hg	136 ± 22	142 ± 23	0.10
Diastolic blood pressure, mm Hg	76 ± 11	78 ± 12	0.52
Uric acid, mg/dl	6.4 ± 1.3	6.1 ± 1.2	0.14
Urea nitrogen, mg/dl	62 ± 17	61 ± 14	0.77
Creatinine, mg/dl	10.3 ± 2.6	9.8 ± 2.4	0.19
Bicarbonate, mEq/liter	18.5 ± 4.7	18.6 ± 4.0	0.90
Urea reduction ratio, %	68.8 ± 7.2	67.5 ± 7.6	0.27
Calcium, mg/dl	9.4 ± 0.6	9.3 ± 0.7	0.66
Phosphorus, mg/dl	7.4 ± 1.8	7.2 ± 1.5	0.61
PTH, median (IQR) pg/ml	230 (137–340)	206 (116–336)	0.53

* Except where indicated otherwise, values are the mean ± SD. Vintage = time since initiation of dialysis; IQR = interquartile range; PTH = parathyroid hormone.

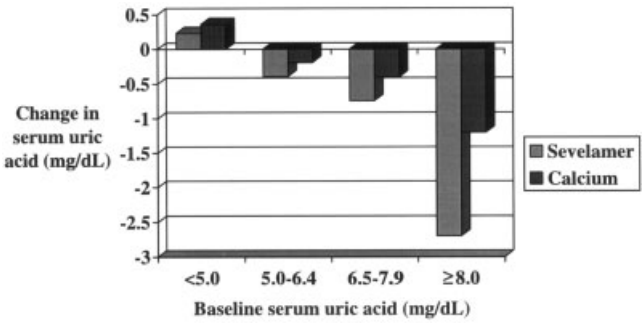

Figure 1. Mean change in serum uric acid levels by baseline concentrations. The numbers of subjects with baseline serum uric acid concentrations of <5.0 mg/dl, 5.0–6.4 mg/dl, 6.5–7.9 mg/dl, and ≥8.0 mg/dl were 20, 85, 49, and 15, respectively.

The change in uric acid concentration (from baseline to the end of the study) was directly correlated with the changes in BUN level (r = 0.36, $P < 0.0001$) and serum creatinine level (r = 0.25, $P = 0.015$), and was inversely correlated with the change in serum bicarbonate level (r = −0.16, $P = 0.03$). The associations among the changes in concentrations of uric acid and other proxies of dietary protein intake were independent of binder assignment.

Multivariable analyses. We used least squares regression to determine the effects of treatment assignment on serum uric acid concentrations while adjusting for potential confounding variables. The adjusted mean change in serum uric acid concentration was −0.72 mg/dl versus −0.15 mg/dl in sevelamer- versus calcium-treated subjects, respectively ($P = 0.001$), corresponding to a relative change of 0.57 mg/dl. The model included the effects of age, sex, diabetes, vintage, dialysis dose, and the changes in BUN and bicarbonate concentrations, and explained 23% of the variation. There were no significant interactions between the effect of binder assignment and other confounding variables (the multiplicative interaction terms were not significant).

Large decrease in uric acid concentration. We a priori considered a reduction in uric acid concentration of −1.5 mg/dl or more to be a clinically significant reduction (20–25% of baseline, depending on sex). Twenty-three percent of sevelamer-treated subjects experienced a study-related reduction in the concentration of uric acid equal to −1.5 mg/dl or more, compared with 10% of calcium-treated subjects ($P = 0.02$). Figure 1 shows the mean change in serum uric acid concentration

Table 2. Previous studies using sevelamer in end-stage renal disease

Study (ref)*	No. of subjects	Duration, weeks	Mean change in uric acid concentration, mg/dl	*P*, within group
GTC-10-201	21	2	−0.3	0.37
GTC-10-202 (17)	36	8	−0.4	0.06
GTC-36-203 (18)		12		
Sevelamer	23		−0.7	0.01
Sevelamer + calcium	27		−0.4	0.045
GTC-36-301 (19)	72	8	−0.4	0.0001
GTC-36-302 (20)	142	8	−0.7	<0.0001
GTC-36-901 (21)	192	44	−0.8	<0.0001

* GTC = Geltex Pharmaceuticals.

by binder assignment and baseline serum uric acid concentration.

DISCUSSION

Gout disproportionately affects persons with chronic kidney disease, since declining GFR leads to hyperuricemia due to reduced urinary clearance of urate. Hyperparathyroidism, a common complication of moderate-to-advanced chronic kidney disease, can also promote hyperuricemia via enhanced urate absorption (4–6). Fortunately for patients undergoing dialysis, hyperuricemia can be attenuated by urate removal, especially when high-flux membranes are used (7).

While serum uric acid concentrations are not consistently associated with the incidence or flares of gout, several studies have noted the relevance of treatment-associated reductions in serum uric acid concentrations. Li-Yu et al followed up 57 subjects with a history of gout who were treated with allopurinol and found that subjects in whom serum uric acid levels were maintained below 6.0 mg/dl showed a depletion of urate crystal stores in their knee joints as well as a reduction in the number of gout attacks (8). In a retrospective study of 350 patients, Yamanaka et al showed that a reduction in uric acid concentration to 4.6–6.6 mg/dl was associated with a 30% reduction in the recurrence of gouty arthritis (9).

Population-based studies have demonstrated an association between elevated serum uric acid concentrations and cardiovascular disease. Results of some studies have suggested that the association may be confounded by other cardiovascular risk factors, although others have shown a more robust, independent association (10,11). Hyperuricemia is especially common in individuals with hypertension and may reflect a decrease in renal blood flow, resulting in enhanced urate reabsorption (12,13). In the Systolic Hypertension in the Elderly Program (SHEP) study, 4,736 men and women age ≥60 years were randomly assigned to receive either a thiazide diuretic or a placebo. Among all subjects, there was a 7% increase in the cardiovascular event rate per mg/dl increase in baseline serum uric acid concentration. Although subjects randomly assigned to receive diuretics had fewer cardiovascular events, the event rate was not reduced in subjects whose serum uric acid concentration increased by ≥1.0 mg/dl, suggesting that the increase in serum uric acid level might have attenuated other treatment-related benefits (14). In contrast, Chamorro et al studied 881 patients presenting with acute ischemic stroke and found a 12% increase in the odds of a favorable outcome per each mg/dl increase in serum uric acid concentration, which they credited to the antioxidant properties of uric acid (15).

More recently, a post hoc analysis of the Losartan Intervention For Endpoint (LIFE) trial suggested that a drug-induced reduction in serum uric acid concentration may decrease the risk of cardiovascular disease. In this trial, 9,193 subjects at high risk for cardiovascular disease were randomly assigned to receive either the angiotensin receptor blocker losartan, which is known to be uricosuric, or the beta-blocker atenolol. Losartan reduced the risk of cardiovascular morbidity and mortality (the primary end point) by 13%. It was estimated that the difference in serum uric acid concentrations between the two groups ($P = 0.004$) might have been responsible for nearly one-third of the overall benefit afforded by losartan (16).

Higher levels of inorganic phosphates, rather than organic phosphates, are associated with higher mortality in patients with ESRD, and sevelamer, a nonabsorbed hydrogel, effectively binds inorganic phosphates in the gastrointestinal tract (17–21). Previous

uncontrolled studies of sevelamer in patients undergoing hemodialysis demonstrated mean within-group reductions in serum uric acid concentrations of ~0.7 mg/dl (range −0.3 mg/dl to −0.8 mg/dl) (Table 2). In the present study, nearly 1 in 4 subjects treated with sevelamer experienced a relatively large reduction in the concentration of uric acid (≥1.5 mg/dl). Moreover, the change in uric acid level was proportional to the severity of hyperuricemia at baseline ($r = -0.49$, $P < 0.0001$), as shown in Figure 1.

The use of nonsteroidal antiinflammatory drugs in the population of patients undergoing dialysis can be complicated by gastrointestinal bleeding, exacerbation of hypertension, and volume retention (22,23). Colchicine has been associated with myoneuropathy, multiorgan failure, cardiorespiratory collapse, bone marrow suppression, and death in patients with kidney disease (24,25) and should be used with extreme caution in persons with an estimated GFR of <30 ml/minute/1.73 m^2. Allopurinol can generally be used safely in chronic kidney disease, although dose adjustments are required due to impaired clearance of the drug's major active metabolite, oxypurinol (26). Given the limitations of existing therapies, it would be beneficial to find alternative agents that could decrease serum uric acid concentrations without a significant risk of adverse events. For patients with advanced chronic kidney disease, hyperphosphatemia, hyperlipidemia, and hyperuricemia, sevelamer would be an excellent therapeutic choice. To date, sevelamer has been approved only for use in patients with advanced chronic kidney disease who are undergoing dialysis. Sevelamer could cause hypophosphatemia in persons with normal kidney function and should not be used in this setting.

In the present study, baseline uric acid concentrations were not associated with the extent of vascular calcification. Moreover, there was no drug-independent association between the change in uric acid concentration and change in vascular calcification (27). It is not known whether hyperuricemia contributes to atherosclerotic and arteriosclerotic vascular disease in chronic kidney disease.

There are several important limitations of this analysis. First, there were no estimates of dietary protein or purine intake. While BUN and bicarbonate are reasonable proxies for protein intake, dietary assessment for purine intake would have been of interest. Notably, while some have recommended a reduction in dietary protein intake for patients with mild-to-moderate chronic kidney disease, patients undergoing hemodialysis are generally advised to ingest ample dietary protein (≥1.2 gm/kg body weight/day) (28). Second, the mechanisms by which serum uric acid concentration is reduced by sevelamer are unknown. While the severity of hyperparathyroidism might be expected to affect uric acid concentrations, the calcium-treated group had significantly lower PTH concentrations, yet higher uric acid concentrations, compared with the sevelamer-treated group. Moreover, there were no differences in BUN or creatinine concentrations or in the efficiency of dialysis between groups, suggesting that the change in uric acid resulted from a decrease in uric acid production rather than an increase in uric acid elimination. Sevelamer might bind uric acid directly, or it could possibly bind guanosine or other guanidino compounds in the purine metabolic pathway. Further research will be required to test these hypotheses. Binding of guanidino compounds by sevelamer would be particularly relevant, given their putative role as uremic toxins (29). Third, the change in serum uric acid concentration was not among the primary outcomes of the parent clinical trial (3). However, the consistent findings of prior studies in concert with the findings presented here suggest that these results are not spurious. Finally, the sample size was insufficient to evaluate a meaningful difference in cardiovascular events or other "hard" outcomes, such as flares of gout, mortality, and hospitalizations.

In summary, in a randomized clinical trial comparing sevelamer and calcium-based phosphate binders, we observed a significant decrease in serum uric acid concentrations among subjects randomly assigned to receive sevelamer. More than 1 in 5 subjects experienced a substantial lowering of serum uric acid concentration, and the reduction was proportional to baseline levels. Additional studies will be required to determine whether sevelamer might lead to fewer flares of gout in affected patients, or whether the hypouricemic effects of sevelamer contribute to its protective effects against vascular calcification.

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