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USE OF SEVELAMER HYDROCHLORIDE AS AN OXALATE BINDER

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Abstract

Purpose—We tested the hypothesis that the cationic phosphate binder sevelamer hydrochloride could reduce hyperoxaluria and calcium oxalate supersaturation in patients with enteric hyperoxaluria by binding fatty acids, binding phosphate and rendering calcium free to bind oxalate, and/or directly binding oxalate. A secondary objective was to assess changes in the urinary excretion of other substances associated with nephrolithiasis.

Materials and Methods—Ten patients with enteric hyperoxaluria were enrolled in a nonrandomized, open-label trial of sevelamer hydrochloride (3200 mg TID for 7 days).

Results—With treatment, the mean urinary oxalate fell 17% (0.84 to 0.70 mmol/day) and the urinary oxalate/creatinine ratio fell 11% (0.055 to 0.049 mmol/mmol); $P=NS$ for both. Urinary calcium increased 25% ($P=NS$). Urinary citrate decreased 23% ($P=0.01$) and urinary phosphorus decreased 44% ($P=0.0001$). Mean supersaturations for calcium oxalate, brushite, hydroxyapatite, uric acid and sodium urate did not change significantly, however, the decrease for brushite approached statistical significance ($P=0.07$). Mean serum phosphorus was 3.6 mg/dl at baseline and 3.3 mg/dl with therapy ($P=NS$). No patient developed hypophosphatemia. One patient dropped out due to abdominal pain.

Conclusions—Sevelamer hydrochloride dramatically decreased urinary phosphorus excretion, with a lesser effect on urinary oxalate. Supersaturation for calcium oxalate did not fall, due to counterveiling effects on other constituents, including an increase in urinary calcium and a decrease in urinary citrate. Although sevelamer hydrochloride may not be an ideal agent for correcting hyperoxaluria, its potential to reduce calcium phosphate supersaturation merits further investigation.

Keywords

Calcium oxalate; enteric hyperoxaluria; fat malabsorption; nephrolithiasis; phosphate binder

INTRODUCTION

Patients with fat malabsorption frequently over absorb oxalate from their diet, a condition called enteric hyperoxaluria. Known potential causes include inflammatory bowel disease¹, jejunoileal bypass^{2–4} or Roux-en-Y bypass surgery for obesity^{5, 6}, gastric ulcer surgery³,

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and as a result of chronic mesenteric ischemia³. In such cases calcium oxalate kidney stones are frequently observed. In addition to the hyperoxaluria, contributing factors include a low urinary citrate concentration, decreased urine volumes, and a low urinary pH, all due to diarrhea and consequent loss of fluid and bicarbonate in the stool⁶. In general the degree of hyperoxaluria correlates with steatorrhea⁷.

Unfortunately, established treatments for enteric hyperoxaluria are not entirely satisfactory. Typically a low oxalate, low fat diet is prescribed in order to reduce oxalate delivery to the colon and to limit fat malabsorption, thereby reducing calcium sequestration and the consequent distal colonic effects of fatty acids and bile acids^{8,9}. Bile acid binding agents such as cholestyramine have met with mixed success^{8,10}. Dietary restriction of oxalate is not always entirely effective since many patients cannot readily identify causative dietary constituents¹¹. Oral calcium is therefore often used as an oxalate binder². Often large doses of calcium are needed, potentially increasing urinary calcium and perhaps reducing the overall effects on urinary calcium oxalate supersaturation.

Sevelamer hydrochloride is a cationic non-absorbable polymer used in the end stage renal disease population as a phosphate binder. We hypothesized that sevelamer hydrochloride might be useful to treat enteric hyperoxalurias via several potential mechanisms: 1) direct binding of oxalate; 2) absorption of bile acids; and 3) by binding phosphate, freeing additional enteric calcium to act as an oxalate binder. Therefore, we conducted an open label pilot study in 10 patients with known enteric hyperoxaluria.

MATERIALS AND METHODS

Patient population

This study was approved by the Mayo Clinic Institutional Review Board. Patients with nephrolithiasis, clinical signs of fat malabsorption and apparent enteric hyperoxaluria were recruited for study from the Mayo Kidney Stone Clinic. Men and women age 18 or greater with the presence of hyperoxaluria (>0.5 mM/day; >45 mg/day) and a gastrointestinal disorder associated with fat malabsorption were eligible. Clinical malabsorptive syndromes sought included inflammatory bowel disease in remission, celiac sprue, gastrointestinal resection resulting in short bowel syndrome (e.g., jejunioileal or gastric bypass for obesity), or chronic pancreatitis. Stone history was confirmed by the presence of radiopaque stones on x-ray, or a history consistent with passage of a stone, stone surgery, or ESWL in the last 2 years. Stone composition was confirmed either by stone analysis demonstrating more than 50% calcium oxalate, or by radiographic demonstration of a calcific renal stone in the presence of hyperoxaluria.

Patients were maintained on previous doses of oxalate binders (e.g., calcium), diet prescriptions (e.g., low oxalate diet), or other stone prevention treatments (e.g., citrate). While oral intake was not specifically controlled, patients were asked to maintain a similar diet during all 2-day urine collections. After informed consent was obtained, two baseline 24-hour urines were collected on consecutive days with a baseline blood sample for electrolytes (Figure 1). Patients then began taking 3,200 mg of sevelamer hydrochloride TID with meals for 7 days. On days 6 and 7 of sevelamer hydrochloride, two repeat 24-hour urines were collected (days 6–7) together with a second blood electrolyte panel.

Urine chemistries

Twenty-four hour urinary concentrations of oxalate, calcium and other determinants of supersaturation were measured in the Mayo Renal Function Laboratory and electrolyte panels

in the Mayo Central Clinical Laboratory. Supersaturations were calculated using the EQUIL2 program ¹².

Statistics

Group means and distributions at each time period were compared by paired T-test using JMP software (SAS Institute Inc., Cary, N.C., USA). P values <0.05 were accepted as significant.

RESULTS

Causes of enteric hyperoxaluria were Roux-en-Y gastric bypass for obesity (n=8), Roux-en-Y gastrojejunostomy for Crohn's disease (n=1) and partial small bowel resection for small bowel obstruction together with partial colonic resection for diverticulitis (n=1). There were equal numbers of men and women (5 each). The mean age was 50.7 ± 10.4 years, with a mean body mass index of 33.09 ± 5.84 kg/m². Amongst the gastric bypass group, the mean time since surgery was 4.6 ± 3.3 years (range 2–12 years). Renal function was preserved in all patients, with a mean serum creatinine of 1.1 ± 0.2 mg/dl (Table 1). In general the medication was well-tolerated. One patient dropped out due to abdominal pain. Mean serum phosphorus was 3.6 mg/dl at baseline and 3.3 mg/dl with therapy (P=NS). No patient developed hypophosphatemia.

With treatment, the mean urinary oxalate fell 17% (0.84 to 0.70 mmol/day) and the urinary oxalate/creatinine ratio fell 11% (0.055 to 0.049 mmol/mmol); P=NS for both (Figure 2). Urinary calcium increased 25% (P=NS), urinary citrate decreased 23% (P=0.01) and urinary phosphorus decreased 44% (P=0.0001). Mean supersaturations for calcium oxalate, brushite, hydroxyapatite, uric acid and sodium urate did not change significantly, however, a decrease for brushite approached statistical significance (P=0.07) (Figure 3).

DISCUSSION

This study demonstrates that a short term oral course of sevelamer hydrochloride dosed TID with meals in a group of patients with enteric hyperoxaluria dramatically decreased urinary phosphorus excretion, with a lesser effect on urinary oxalate. Supersaturation for calcium oxalate did not fall, due to countervailing effects on other constituents that included an increase in urinary calcium and a decrease in urinary citrate. Therefore, sevelamer hydrochloride may not be an ideal agent for correcting hyperoxaluria in this patient group.

Hyperoxaluria is a well-known complication of chronic fat malabsorption. It is thought that there is increased delivery of fats to the colon where they combine with free calcium, thereby allowing unbound oxalate to pass through the colonic mucosa ². Colonic permeability may also be increased by these malabsorbed fatty acids and bile acids. Recently, experiments in knockout mice suggest that colonic secretion of oxalate may also be an important pathway for oxalate elimination ¹³. It is unknown if these transporters might be affected under states of fat malabsorption, or if they could represent novel treatment targets. Under any of these scenarios, oxalate complexation within the colonic mucosa should reduce urinary oxalate excretion, either by favoring oxalate secretion into the colonic lumen, or decreasing its availability for absorption. Indeed, our study suggests that sevelamer hydrochloride could modestly reduce urinary oxalate levels via at least one of these mechanisms. However, the positive effects on urinary oxalate levels were offset by an overall decline in urinary citrate together with a more modest increase in urinary calcium. The former is likely due to the acid load associated with sevelamer hydrochloride ingestion. The underlying reasons for the rise in urinary calcium levels are less clear, but may be related to complexes formed by the cationic sevelamer in the colonic lumen, e.g., with phosphorous, that effectively increase bioavailability of calcium for absorption, or due to effects of the acid load on bone. Therefore the overall effect of sevelamer hydrochloride on calcium oxalate supersaturation was neutral in this patient group. It is not

known whether additional medications, e.g., potassium citrate, could be added to sevelamer hydrochloride to counterbalance its acid load and negative effect on urinary citrate levels. It is also possible that concurrent adjustments in other medications (e.g., calcium binders or supplements) could be considered to achieve an overall more favorable change in urinary supersaturation.

Not unexpectedly, the most dramatic effect of sevelamer hydrochloride was to reduce urinary phosphorus levels by 44% (Figure 2). This, together with a slight fall in urinary pH, resulted in a slight fall in urinary Brushite supersaturation that was of borderline significance (-1.3 to -2.0 DG; $P=0.07$; Figure 3). Further, calcium in the urine increased slightly, perhaps indirectly related to phosphate binding in the gut (and increased calcium bioavailability for absorption), or alternatively secondary to effects of lower serum phosphorous on Vitamin D and parathyroid hormone levels. Calcium phosphate stones are not typically associated with enteric hyperoxaluria, as reflected by the relatively low baseline calcium phosphate supersaturation. However, in patients with calcium phosphate stones, a similar magnitude of decrease in urinary phosphorous, pH and Brushite supersaturation could be of clinical significance. Therefore, the potential use of sevelamer hydrochloride to reduce calcium phosphate supersaturation in other patient groups merits further investigation, although this would require careful long term study and follow-up with regard to overall calcium and phosphorous balance.

Sevelamer hydrochloride has been used indefinitely in patients with chronic kidney disease and end stage renal failure without significant toxicity. However, the effects of long-term sevelamer hydrochloride on phosphate balance in the absence of renal dysfunction are unknown. Indeed, we did observe a slight but statistically insignificant fall in serum phosphorous in this short term study. Therefore, any long term trial of sevelamer hydrochloride would require careful attention to phosphorous homeostasis.

A weakness of this study was the lack of a rigorously controlled diet in a clinical research center setting. However, patients were clinically stable and duplicate urines were collected at both time points in an attempt to average out any day-to-day variation. Further, the outcome studied was urinary supersaturation, rather than stone events. However, trials using stone disease as an endpoint typically require up to 3 years follow-up, and urinary supersaturation does correlate with stone risk and composition¹⁴.

In conclusion, amongst this small group of enteric hyperoxalurics, sevelamer hydrochloride dramatically decreased urinary phosphorus excretion, with a lesser effect on urinary oxalate levels. Supersaturation for calcium oxalate did not fall, due to countervailing effects on other constituents, including an increase in urinary calcium and a decrease in urinary citrate. Therefore, sevelamer hydrochloride may not be an ideal agent for correcting hyperoxaluria in this patient group. The potential to reduce calcium phosphate supersaturation merits further investigation in other stone forming patient groups, although the effects of long-term sevelamer hydrochloride on phosphate balance in the absence of renal dysfunction are unknown.

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Abbreviations

ESWL

extracorporeal shock wave lithotripsy

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Figure 1. Study design

Patients had blood (1) and 24-hr urine collections (2) before and after a 7 day course of sevelamer hydrochloride (3200 mg TID).

24 Hour Urinary Excretion (% Change)

Figure 2. Mean twenty-four hour urine excretions (% change)

A slight fall in oxalate (17%) and increase in calcium (24%) excretion was not statistically significant. However declines in urinary excretions of citrate (23%) and phosphorous (44%) were (**P<0.01, ***P<0.001 vs. baseline).

Figure 3. Calculated urinary supersaturations in patients before and after treatment with sevelamer hydrochloride

A slight increase in mean calcium oxalate SS was not significant, whereas a fall in Brushite SS approached statistical significance ($P=0.07$).

Table 1

Summary of mean serum and urinary changes for 10 enteric hyperoxaluric patients before and at the end of one week on Sevelamer hydrochloride.

	Before Sevelamer	During Sevelamer	P
<u>Serum</u>			
Sodium (mmol/L)	140 ± 2	140 ± 4	0.21
Potassium (mmol/L)	4.5 ± 0.2	4.3 ± 0.4	0.12
Calcium (mg/dl)	9.1 ± 0.5	9.2 ± 0.3	0.21
Phosphorus (mg/dl)	3.6 ± 0.7	3.3 ± 0.5	0.16
Uric Acid (mg/dl)	4.8 ± 0.7	5.1 ± 0.7	0.37
Creatinine (mg/dl)	1.1 ± 0.2	1.1 ± 0.2	1.00
Blood Urea Nitrogen (mg/dl)	18 ± 3	18 ± 3	0.83
Chloride (mmol/L)	105 ± 3	105 ± 5	0.88
Bicarbonate (mmol/L)	26 ± 2	24 ± 2	0.09
Magnesium (mg/dl)	1.9 ± 0.2	1.9 ± 0.2	0.56
<u>Urine</u>			
Volume (ml/24 hrs)	2250 ± 1509	2205 ± 1312	0.76
Osmolality (mosm/kg)	591 ± 244	561 ± 207	0.41
pH	6.0 ± 0.7	5.8 ± 0.9	0.30
Citrate (mg/24 hrs)	512 ± 615	396 ± 517	0.01
Oxalate (mmol/24 hrs)	0.84 ± 0.39	0.70 ± 0.33	0.23
Sodium (mmol/24 hrs)	247 ± 118	220 ± 104	0.46
Potassium (mmol/24 hrs)	88 ± 52	91 ± 60	0.62
Calcium (mg/24 hrs)	107 ± 95	133 ± 116	0.11
Phosphorus (mg/24 hrs)	1291 ± 374	720 ± 317	0.0001
Uric Acid (mg/24 hrs)	589 ± 179	545 ± 184	0.50
Creatinine (mg/24 hrs)	1784 ± 767	1726 ± 669	0.88
Sulfate (mmol/24 hrs)	21 ± 6	20.3 ± 10	0.89
Magnesium (mg/24 hrs)	124 ± 69	121 ± 69	0.94
<u>Calcualted supersaturation</u>			
Calcium Oxalate (DG)	1.6 ± 0.9	1.8 ± 1.0	0.18
Brushite (DG)	-1.3 ± 0.8	-2.0 ± 1.2	0.07
Hydroxyapatite (DG)	2.3 ± 1.9	1.5 ± 2.1	0.20
Uric Acid (DG)	0.1 ± 4.2	0.9 ± 4.3	0.20
Sodium Urate (DG)	1.2 ± 1.1	0.9 ± 1.0	0.10

Values are mean (SE).