Kidney International, Vol. 66 (2004), pp. 676–682

ION CHANNELS – MEMBRANE TRANSPORT – INTEGRATIVE PHYSIOLOGY

Fat malabsorption induced by gastrointestinal lipase inhibitor leads to an increase in urinary oxalate excretion

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Fat malabsorption induced by gastrointestinal lipase inhibitor leads to an increase in urinary oxalate excretion.

Background. Unabsorbed fat and bile acids may react with calcium in the intestinal lumen, limiting the amount of free calcium binding with oxalate and thereby raising intestinal oxalate absorption leading to hyperoxaluria. The aim of the present study was to determine whether orlistat (Xenical®), a gastrointestinal lipase inhibitor, might increase urinary oxalate in an experimental rat model.

Methods. Thirty-nine male adult Wistar rats were fed a standard diet alone (controls) or supplemented with either 2% sodium oxalate (NaOx) or 3.2 mL of soy oil, or with both (NaOx + soy oil) for 4 weeks (diet period). Orlistat (16 mg/day) was added to the diet from the 5th to the 8th week (diet + orlistat period). Urinary oxalate (uOx), calcium (uCa), magnesium (uMg), and citrate (uCit) were determined and the ion-activity product of calcium oxalate [AP (CaOx) $index_{rat}$] was estimated.

Results. Compared to baseline uOx significantly increased after diet + orlistat in controls (0.64 ± 0.1 mg/24 hours vs. 0.56 ± 0.1 mg/24 hours), soy oil (0.80 ± 0.3 mg/24 hours vs. 0.49 ± 0.2 mg/24 hours), and NaOx (2.48 ± 0.8 mg/24 hours vs. 0.57 ± 0.2 mg/24 hours), but the most marked increase occurred in NaOx + soy oil (3.87 ± 0.7 mg/24 hours vs. 0.47 ± 0.1 mg/24 hours). All groups except controls presented a significant reduction in uCa and uMg. Orlistat induced a significant increase in AP (CaOx) $index_{rat}$ compared, respectively, to baseline and to the diet period in NaOx (4.52 ± 2.34 mg/24 hours vs. 0.94 ± 0.86 and 1.53 ± 0.93 mg/24 hours) and NaOx + soy oil (6.49 ± 4.03 mg/24 hours vs. 0.54 ± 0.17 and 1.76 ± 1.32 mg/24 hours).

Conclusion. These data suggest that the use of lipase inhibitors, especially under a diet rich in oxalate alone or associated with fat, leads to a significant and marked increase in urinary oxalate and a slight reduction in uCa and uMg that, taken together, resulted in an increase in AP (CaOx) $index_{rat}$, elevating the risk of stone formation.

Hyperoxaluria is one of the major risk factors for calcium oxalate stone formation due to urinary calcium oxalate (CaOx) supersaturation, since the latter is directly correlated with urinary oxalate (uOx) concentration [1–3].

In healthy individuals, most of the uOx derives from hepatic synthesis and enzymatic conversion of ascorbic acid, with between 10% and 50% being provided by dietary intake [4, 5].

Clinically, hyperoxaluria can be due to an enzymatic disturbance in oxalate biosynthesis (primary hyperoxaluria type I and II, or pyridoxine deficiency), but primary hyperoxaluria type I, the prevailing type, is a very rare autosomal-recessive disorder [6, 7]. Secondary hyperoxaluria is due to either increased availability of substrate (ascorbic acid, ethylene glycol, methoxyflurane) [8] or to intestinal hyperabsorption of oxalate caused by a high oxalate diet, enteric hyperoxaluria, or an imbalance between intraluminal calcium and oxalate as in a low-calcium diet [9–13].

Enteric hyperoxaluria induced by fat and bile salt malabsorption is the hallmark of hyperoxaluria due to intestinal hyperabsorption of oxalate. The gastrointestinal diseases that have been associated with this entity are those characterized by an absence or nonfunction of the small bowel (enteritis, small bowel resection, or bypass surgery) and those causing defective absorption of fat or bile acids (chronic pancreatitis, biliary cirrhosis, blind loop syndrome, and other diseases) [14–17]. Unabsorbed bile acids and fatty acids may react with calcium in the intestinal lumen, forming "soaps" that limit the amount of free calcium binding with oxalate, with a consequent increase in intestinal oxalate absorption leading to hyperoxaluria [14, 18–23]. It has also been shown that bile acids may directly increase the colonic permeability to oxalate [24, 25].

Orlistat, a chemically synthesized derivative of the natural product lipstatin originally isolated from *Streptomyces toxytricini*, is a specific inhibitor of pancreatic and gastric lipases [26] used to reduce body weight in humans [27, 28].

We hypothesized that fat malabsorption induced by a gastrointestinal lipase inhibitor and the excess of bile

Key words: orlistat, fat, bile acids, hyperoxaluria, urinary supersaturation.

Received for publication June 30, 2003
and in revised form January 20, 2004, and February 9, 2004
Accepted for publication March 1, 2004

salts could complex with calcium and reduce the formation of CaOx insoluble compounds in the intestinal lumen, hence raising free oxalate absorption and leading to hyperoxaluria.

METHODS

Study protocol

Thirty-nine male Wistar rats weighing 230 to 320 g, kept in individual cages for 8 weeks, were divided into four groups according to the diet administered: standard chow containing 1.02% calcium, 0.80% phosphorus, 0.35% magnesium, 1.07% potassium, 0.27% sodium, and 5.2% fat/g (controls, $N = 10$), or supplemented with sodium oxalate (NaOx) added at 2.0% concentration (NaOx group, $N = 10$), or with 3.2 mL soy oil to increase the amount of lipids in the diet (soy oil group, $N = 9$), or supplemented with both (NaOx + soy oil group, $N = 10$). The supplements were mixed with the powdered diet. Rats were given access to 20g/day of the ground diet during the whole period of the experiment except for the day in which feces and urine were collected (see explanation below). From the 5th week to the end of the experiment, all groups received a daily single oral dose of 16 mg (800 mg/kg of chow) of orlistat (Xenical®) [29, 30], which was mixed with the diet. Rats that ate less than 16 g of food were not included in the study.

Feces for the measurement of the percentage of fat, and 24-hour urine samples for the measurement of urinary volume, uOx, calcium (uCa), magnesium (uMg), citrate (uCit), sodium (uNa), potassium (uK), creatinine (uCreat), and urinary pH (upH), were obtained at baseline and after 4 weeks to assess the effect of diet alone (diet period), and after 8 weeks to assess the effect of diet plus orlistat (diet + orlistat period). Forty-eight hours before feces and urine collection, the rats were placed in metabolic cages for adaptation. On the collection day, the NaOx supplements were given by gavage to prevent contamination of urine samples with chow containing oxalate. The experimental protocol was approved by the Ethics Committee for Animal Experiments of Universidade Federal de São Paulo.

Urinary parameters

The urine samples were divided into 2 aliquots: one containing 6 N HCl (20 mL/L) for measurements of uOx, uCa, uCit, and uMg, and the other placed in a dry container for upH, uNa, uK, and uCreat determination. Calcium was determined by atomic absorption spectrophotometry (Perkin Elmer Atomic Spectrophotometer 290-B) (Norwalk, CN, USA); oxalate by an enzymatic method [31] using the Sigma Oxalate Diagnostic Kit (Sigma Chemical Co., St Louis, MO, USA), and sodium and potassium by flame photometry (B-462–Micronal). Creatinine was determined by Jaffe's method [32], magnesium was determined by combination with calmagite (Labtest Diagnostics Kit) (Minas Gerais, Brazil) and citrate by an enzymatic assay using citrate lyase [33]. Urinary pH was determined with a pH universal tape (pHydrion Paper Dispenser) (Micro Essential, NY, USA).

Feces

Percent fecal fat was quantified by the steatocrit technique [34–37], which is based on a calculation that considers the liquid part [fatty layer (F)] and solid part [solid layer (S)] in isolated excrement samples, according to the formula: steatocrit (percent of fat in feces) = $[F \div (S + F)] \times 100$. The steatocrit measurement was performed twice in each fecal sample, and the mean of two measurements was then considered.

Ion-activity product

The ion activity product of CaOx [AP (CaOx) $index_{rat}$] was calculated based on the urinary values of uOx, uCa, uMg, uCit, and volume according to the following formula: $[(4067 \times Ca^{0.93} \times Ox^{0.96}) \times (Mg^{-0.55} \times (Cit + 0.015)^{-0.60} \times V^{-0.99})]$, derived from AP (CaOx) Tiselius Index, originally used for human urine [38]. The adaptation for rat urine has been based on average urine composition obtained from literature [39] and our own analytical data. The relative effect of each urine variable was assessed by means of an iterative computerized approximation with the Equil 2 program [40]. There was a good correlation ($r = 0.89$) between AP (CaOx) $index_{rat}$ calculated by our recently published adapted formula [41] and AP (CaOx) as derived from Equil 2.

Histologic analysis

At the end of the study, the kidney of two rats from each group was removed under ether anesthesia, cut longitudinally and fixed with 10% formaldehyde for hematoxylin and eosin staining. Crystal deposition in renal tissue was searched under polarized light microscopy. A case of a kidney transplanted patient who developed acute tubular necrosis with heavy CaOx tubular deposition was used as a positive control.

Statistical analysis

With the exception of citrate and magnesium, none of the parameters presented a normal curve distribution, according to the Kolmogorov-Smirnov test. Therefore, only nonparametric tests were employed. The Friedman's test was used to compare the results between baseline, diet, and diet + orlistat within each group, and the Kruskal-Wallis, complemented by Dunn's test was used to compare the results between groups in the same period. The

Table 1. Urinary parameters mean values at baseline, after diet and diet + orlistat periods

Urinary parameters	Groups			
	Control	Soy oil	Sodium oxalate (NaOx)	Sodium oxalate (NaOx) + soy oil
Volume *ml*				
Baseline	11.1 ± 5.0[d]	17.4 ± 2.9	10.5 ± 3.5[d]	11.3 ± 1.2[d]
Diet	11.7 ± 4.9	6.8 ± 1.6[a,c]	5.4 ± 1.7[a,c]	5.7 ± 2.2[a,c]
Diet + orlistat	16.0 ± 5.5	9.1 ± 3.3[a,c]	5.5 ± 1.5[a,c,d]	6.5 ± 2.3[a,c,d]
Oxalate *mg/24 hours*				
Baseline	0.56 ± 0.1	0.49 ± 0.2	0.57 ± 0.2	0.47 ± 0.1
Diet	0.49 ± 0.1	0.87 ± 0.4[a,c]	1.60 ± 1.3[a,c]	3.13 ± 0.9[a,c,d,e]
Diet + orlistat	0.64 ± 0.1[a,b]	0.80 ± 0.3[a,c]	2.48 ± 0.8[a,b,c,d]	3.87 ± 0.7[a,c,d,e]
Calcium *mg/24 hours*				
Baseline	0.26 ± 0.1[d,e]	0.49 ± 0.0	0.39 ± 0.1	0.38 ± 0.0[c]
Diet	0.31 ± 0.1	0.31 ± 0.0[a]	0.08 ± 0.0[a,c,d]	0.04 ± 0.0[a,c,d,e]
Diet + orlistat	0.45 ± 0.1	0.38 ± 0.1[a]	0.08 ± 0.0[a,c,d]	0.16 ± 0.0[a,c,d]
Citrate *mg/24 hours*				
Baseline	10.5 ± 9.9	14.8 ± 4.2	14.4 ± 8.8	14.1 ± 5.3
Diet	13.8 ± 4.0	8.8 ± 2.3[a]	9.1 ± 7.2	12.7 ± 9.6
Diet + orlistat	17.0 ± 2.9	12.1 ± 4.7[c]	6.2 ± 5.5[a,c,d]	10.3 ± 6.3[c]
Sodium *mEq/L*				
Baseline	0.7 ± 0.3	0.9 ± 0.2	0.6 ± 0.1	0.6 ± 0.1
Diet	0.4 ± 0.1	0.8 ± 0.2[c]	2.5 ± 1.0[a,c,d]	2.9 ± 1.7[a,c,d]
Diet + orlistat	0.4 ± 0.3	1.0 ± 0.3[c]	3.4 ± 1.1[a,c,d]	2.1 ± 0.7[a,c,d]
Magnesium *mg/24 hours*				
Baseline	1.9 ± 1.0	2.6 ± 0.9	1.9 ± 0.5	2.1 ± 0.4
Diet	2.2 ± 0.2	1.4 ± 0.3[a,c]	0.7 ± 0.3[a,c,d]	0.7 ± 0.3[a,c,d]
Diet + orlistat	1.5 ± 0.4	1.6 ± 0.6[a]	0.5 ± 0.2[a,c,d]	1.0 ± 0.3[a,c,d]
Potassium *mEq/L*				
Baseline	1.0 ± 0.2	1.1 ± 0.3	0.9 ± 0.4	0.8 ± 0.1
Diet	0.9 ± 0.2	2.0 ± 0.2[a,c]	1.5 ± 0.8[a,c]	1.7 ± 0.9[a,c]
Diet + orlistat	1.2 ± 0.8	2.4 ± 0.4[a,c]	2.1 ± 0.8[a,c]	2.8 ± 0.5[a,b,c,d,e]
Creatinine *mg/24 hours*				
Baseline	6.2 ± 1.4	8.3 ± 1.0[c]	7.6 ± 3.2[c]	8.0 ± 1.9[c]
Diet	8.9 ± 2.5[a]	11.0 ± 2.0[a,c,e]	5.1 ± 2.3	8.9 ± 3.6[e]
Diet + orlistat	9.9 ± 3.5[a]	10.5 ± 0.9[a,c]	5.8 ± 1.2	7.2 ± 1.9[d,e]
pH				
Baseline	6.9 ± 0.3	6.3 ± 0.3	6.7 ± 0.1	6.6 ± 0.2
Diet	6.8 ± 0.4	6.6 ± 0.4	7.0 ± 0.8	6.5 ± 0.8
Diet + orlistat	6.7 ± 0.4	6.5 ± 0.4	6.9 ± 0.3	6.5 ± 0.4

Data are presented as mean ± SD.
Comparison between periods. [a] $P < 0.05$ vs. baseline; [b] vs. diet.
Comparison between groups: different from ($P < 0.05$): [c] vs. Control; [d] vs. Soy Oil; [e] vs. NaOx.

results are presented as mean ± SD and the level of significance was defined as $P < 0.05$.

RESULTS

Fecal fat and body weight

At baseline, the fecal fat was undetectable in all groups and continued to be so in both control and NaOx groups in diet and diet + orlistat periods. After orlistat use fecal fat was increased to markedly high levels compared both to the diet or baseline periods in soy oil group (22.7 ± 9.4% vs. 7.6 ± 1.3% vs. 0) and also in NaOx + soy oil group (35.1 ± 11.4% vs. 9.8 ± 3.1% vs. 0), respectively. As the gavaging of fat could have influenced the degree of fat malabsorption due to a high amount of fat given all at once, we performed an additional experiment in ten rats that received orlistat plus fat mixed with the diet, rather than gavaged, during 4 weeks, including the collection day. As the mean steatocrit in this group was 26%, a similar result compared to that obtained in the main protocol, we considered that fat malabsorption occurred irrespective of the form of fat supplementation and did not perform additional urinary determinations in this group.

After diet + orlistat period all groups presented a significant mean weight gain compared both to diet or baseline periods. Weight gain had been greater in the groups that had received soy oil in the diet, despite of the presence of fat malabsorption (soy oil 340 ± 16 g vs. 328 ± 15 g vs. 253 ± 87 g; NaOx + soy oil 360 ± 30 g vs. 339 ± 23 g vs. 271 ± 21 g).

Urinary parameters

Table 1 shows the mean values of urinary volume, uOx, uCa, uMg, uCit, uNa, uK, uCreat, and upH at baseline and after the diet and diet + orlistat periods. After diet +

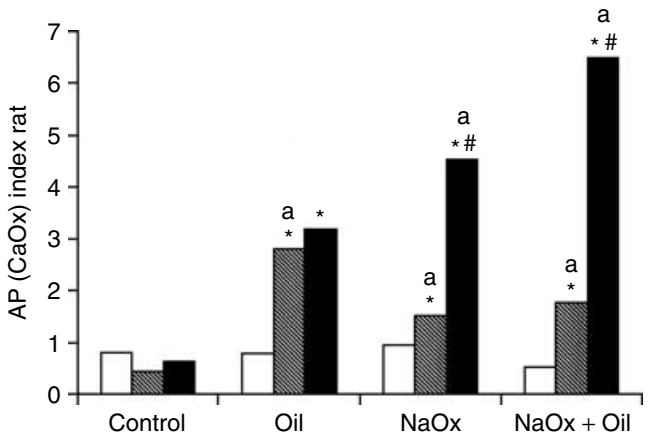

Fig. 1. Mean ion-activity product of calcium oxalate [AP (CaOx) index$_{rat}$] in baseline (□), diet period (▨), and diet + orlistat period (■). $P < 0.05$. *Different from baseline; #Different from diet period; [a]Different from controls.

orlistat period, the mean urinary volume was significantly lower in all groups except for controls, compared to baseline. Baseline mean urinary volume was significantly higher in soy oil vs. all other groups. The NaOx, soy oil, and NaOx + soy oil groups presented a significantly lower mean urinary volume compared to the control group after orlistat use.

After the diet + orlistat period, the mean uOx excretion was higher in all groups compared to baseline. In the NaOx group, the increase was significantly different compared to the diet period as well. Baseline mean values of uOx did not differ between groups. Comparing the values of uOx excretion between groups after diet + orlistat period, mean uOx was markedly and significantly higher in theNaOx + soy oil group vs. NaOx vs. soy oil vs. controls.

A significant decrease in mean uCa was observed in all groups except for controls after the diet + orlistat period compared to baseline. Baseline mean uCa was significantly lower in controls vs. all other groups. After the diet + orlistat period, the NaOx and NaOx + soy oil groups presented a significantly lower mean uCa compared to the controls and soy oil group.

A significant decrease in mean uCit after orlistat use compared to baseline was only observed in the NaOx group. Baseline uCit did not differ between groups. After the diet + orlistat, a significantly lower mean uCit was observed in all groups compared to controls.

With respect to mean uNa, after the diet + orlistat an increase was observed in both groups that received NaOx in the diet (NaOx and NaOx + soy oil), compared to the baseline period. Baseline mean uNa did not differ between groups. Mean uNa was significantly higher in the NaOx and NaOx + soy oil groups than in the controls and soy oil group, and significantly higher in thesoy oil group than in the control group after the diet + orlistat period.

There was a significant decrease in mean uMg in all groups but not in controls, after the diet + orlistat period compared to baseline. Baseline mean uMg did not differ between groups, but after the diet + orlistat there was a significant reduction in uMg in groups that received NaOx in the diet compared to the controls and soy oil group.

A significant increase in mean uK excretion after the diet + orlistat period was observed in all groups except for controls, compared to baseline. Baseline uK did not differ between groups. All three groups differed from controls after the diet + orlistat period. The NaOx + soy oil group presented a higher mean uK compared not only to controls but also to the NaOx and soy oil groups.

Mean uCreat excretion was significantly higher in the soy oil and control groups after the diet + orlistat period versus baseline. Baseline mean uCreat was higher in all groups vs. controls. After the diet + orlistat, a higher mean uCreat concentration was observed in the soy oil and NaOx + soy oil groups compared to the NaOx group, with the soy oil group value being also significantly higher compared to the NaOx + soy oil group.

There were no differences in mean upH between any periods of the study or between groups.

AP (CaOx) index$_{rat}$

After the diet + orlistat, a significant increase in mean AP (CaOx) index$_{rat}$ was observed in the NaOx group compared both to baseline and to the diet period, and also in the NaOx + soy oil group compared both to baseline and to the diet period (Fig. 1). Baseline mean AP (CaOx) index$_{rat}$ did not differ between groups. A higher AP (CaOx) index$_{rat}$ value was observed in all groups compared to controls after the diet + orlistat period, except for the soy oil group, in which the increase was only significant after the diet period.

Histologic analysis

No CaOx crystal deposition or stones were detected in the renal tissues under polarized light microscopy in any of the groups.

DISCUSSION

Intestinal hyperabsorption of oxalate caused solely by high oxalate intake is controversial [5, 42–44] but the imbalance between intraluminal calcium and oxalate caused by a low-calcium diet, absorptive hypercalciuria, or enteric hyperoxaluria is incontrovertible [10, 13, 45].

In enteric hyperoxaluria, malabsorbed fat reacts with calcium reducing the formation of CaOx-insoluble compounds in the intestinal lumen, hence raising free oxalate absorption [14–17]. Several authors have reported that

increasing dietary fat also leads to increased bile salt synthesis in rats [46–48]. The present study aimed to determine whether the use of gastrointestinal lipase inhibitors would induce fat malabsorption, and a surfeit of bile salts with calcium-chelating properties, leading to a secondary hyperabsorption of oxalate.

Our results showed that the use of lipase inhibitors combined with a diet rich in oxalate associated or not with fat leads to an increase in uOx excretion.

Orlistat has been administrated during 4 weeks [29, 49, 50] because our main purpose was to examine the effects of the drug, commonly taken on a long-term basis, upon oxalate excretion, urinary crystallization, and risk of stone formation.

Since the use of gastrointestinal lipase inhibitors in our animal model would not cause fat malabsorption, per se, soy oil was added to the diet for some groups so that 35% of the energy would derive from fat [30, 50]. In order to increase the amount of oxalate available for absorption and subsequent excretion, oxalate was further supplemented in some groups, in amounts already described in the literature [43].

To ensure that fat malabsorption did occur, we measured fecal fat by the steatocrit technique, that despite of not being the gold-standard method [51] is much easier to perform and commonly utilized in human studies [34–37]. However, we are aware that the method is subjective [34], not standardized in rats and should be rather considered a qualitative than quantitative method.

With increasing dietary fat, as evidenced in the groups that received soy oil, there was an increase in fecal fat excretion, which was further enhanced by the use of lipase inhibitor. The higher fecal fat observed in NaOx + soy oil group after the diet + orlistat period remained unexplained but it might have been ascribed to the highly variable reduction of fat absorption induced by orlistat in rodents, ranging from 20% to 80% [49].

In clinical studies, many investigators have suggested that dietary fat is directly correlated with oxalate excretion [52–54]. In the present experiment, the oil supplement lead to a significant increase in uOx excretion. However, the use of lipase inhibitors did not induce a further increase in oxaluria, provided that dietary oxalate was not being concomitantly offered in the diet. Thus, when only oxalate was supplemented, it produced a threefold significant increase in uOx, similar to the findings of Bushinski et al [43] who observed values of uOx twice higher in hypercalciuric rats after oxalate loading for 6 weeks. We observed that the use of orlistat induced a further increase in oxaluria of almost fourfold compared to baseline, even in the absence of fat. This elevation in uOx was also significantly higher in comparison to the period of diet alone. When both oxalate and oil supplements were given, the increment in oxaluria reached six times the baseline value, characterizing an additive effect due to the concomitant presence of fat and excessive bile salts in the intestinal lumen reacting with calcium and also increasing colonic permeability to oxalate which further enhanced free oxalate hyperabsorption. Finally, with the addition of orlistat, uOx levels became eightfold higher than at baseline.

Concerning calcium excretion, we observed that as dietary oil was increased, a fall in uCa took place, probably due to binding with calcium, regardless of the use of orlistat. The supplementation of oxalate alone or associated with orlistat use was accompanied by a fivefold fall in uCa secondary to oxalate binding and the formation of an unabsorbable solid phase of CaOx, confirming the presence of an inverse relationship between colonic oxalate and calcium as previously suggested by several investigators [4, 10, 11, 13, 42, 55, 56]. Orlistat did not further reduce urinary calcium when both fat and oxalate were supplemented.

We observed that increasing dietary oxalate also caused a threefold reduction in uMg. Such reduction was higher than the one found by da Silva et al [57], who employed lower amounts of oxalate. This can be explained by the complexation of oxalate with magnesium in the intestinal lumen limiting the amount of free magnesium for intestinal absorption, hence leading to lower magnesium excretion [57–59]. We also noticed that the oil supplementation alone reduced uMg possibly due to magnesium binding with fat and bile salts in the intestinal lumen forming soaps and decreasing absorption [60]. Orlistat did not further decrease uMg.

There was a trend, albeit not significant, to a reduction of uCit in all groups receiving either NaOx- or NaOx + soy oil-supplemented diets. This lower uCit seemed to parallel the decreases on uMg. According to McConnel et al [17], the lower the availability of magnesium in the renal tubule to bind citrate with, the higher the amount of citrate left for reabsorption resulting in lowered uCit levels.

As expected, uNa increased in the groups that received a NaOx supplement. This increase in uNa should have increased uCa as well [61, 62] but, as reported, uCa fell in the oxalate-loaded rats, indicating that the effect of oxalate on intestinal calcium binding was stronger than the calciuric effect of sodium. Increases in uK excretion paralleled the increases in uNa, probably resulting from the higher delivery of sodium to the distal and collecting tubules that act as a stimulus for potassium secretion at these sites [63].

In our model of normal rats, no crystals or stones were detected in any group, probably because CaOx urolithiasis is not a spontaneous phenomenon in rats [2], even when uOx is increased. It has been extensively shown by the group of Bushinsky et al [43, 64, 65] that the formation of CaOx stones in hypercalciuric rats was only possible when hydroxyproline or ammonium chloride was added

to the diet. However, in the present experimental setting, it was important to determine levels of supersaturation in urine in order to assess if the resulting changes in urinary parameters would represent a risk for stone formation. Simplified estimates of the ion activity product of CaOx, AP (CaOx) index, have been previously developed for human urine [38] and present a good correlation with the classical Equil 2 program [40]. A derivation of this index has been recently adapted to rat urine by Tiselius, Ferraz, and Heilberg [41]. This estimated AP (CaOx) $index_{rat}$, based on the results of uOx, uCa, uMg, uCit, and volume, helped us to address whether or not the use of gastrointestinal lipase inhibitors would interfere with the urinary crystallization risk.

Orlistat induced a tremendous and significant increase in AP (CaOx) $index_{rat}$ in the groups that received either oxalate or fat plus oxalate in the diet. The increase in CaOx supersaturation was three times higher in the NaOx group and 3.5 times higher in the NaOx + soy oil group than that produced by the diet. A significant decrease in urinary volume and a similar reduction in citrate and magnesium after orlistat observed in all groups could have contributed to the increase in AP (CaOx) $index_{rat}$ per se. However, the marked and unique increase in uOx observed mostly in NaOx + soy oil group might have been the main factor responsible for such a high AP (CaOx) $index_{rat}$ in this group, even considering the fall in uCa.

CONCLUSION

These data suggest that the use of lipase inhibitors, especially under a diet rich in oxalate associated or not with fat, leads to a significant and marked increase in uOx and a slight reduction in uCa and uMg that, taken together, resulted in an increase in AP (CaOx) $index_{rat}$, elevating the risk of stone formation.

ACKNOWLEDGMENTS

Research supported by grants from Coordenação de Aperfeiçoamento Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Fundação Oswaldo Ramos. The authors wish to express their thanks to Mirian Aparecida Boim, Ph.D., Alessandra Calábria Baxmann, Ms.C., and Sender Jankiel Miszputen, M.D., for a critical advice on this research and to Maria Ivani Zanon and Silvia Regina Silva Moreira for helpful technical assistance. Portions of this study were presented at the 35th Annual Meeting of the American Society of Nephrology, Philadelphia, Pennsylvania, USA, October 2002.

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