

Nephrolithiasis and Nephrocalcinosis From Topiramate Therapy in Children With Epilepsy



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Introduction: Adults treated with topiramate may develop nephrolithiasis, but its frequency in children on topiramate is unknown. Topiramate inhibits renal carbonic anhydrase, which can lead to renal tubular acidosis and hypercalciuria. We studied 40 consecutive children who initiated topiramate therapy for seizures between January 1997 and February 2003, followed for a mean of 36 months.

Methods: Serum electrolytes, urinary calcium/creatinine ratios, and renal ultrasonography were performed before topiramate and every 6 months thereafter.

Results: Four children developed nephrolithiasis and/or nephrocalcinosis, which resolved on discontinuation of topiramate. In 40 patients, the mean urinary calcium/creatinine ratio increased over time ($P < 0.001$). The mean serum bicarbonate in 40 patients decreased over time ($P < 0.01$). Twenty-three children had urinary calcium/creatinine ratios before topiramate. Nine children with baseline hypercalciuria (defined as urinary calcium/creatinine >0.21) were compared with the 14 children with baseline normal urinary calcium excretion. A greater increase in urinary calcium/creatinine ratios occurred in hypercalciuric children ($P < 0.001$) and a greater decrease in serum bicarbonate levels occurred in the hypercalciuric children ($P < 0.05$) compared with children with baseline normal calcium excretion. Greater urinary calcium excretion was associated with increasing doses of topiramate ($P = 0.039$).

Conclusion: Our study shows that long-term therapy with topiramate in children is associated with persistent hypercalciuria and metabolic acidosis, which can lead to nephrocalcinosis and/or nephrolithiasis. All children initiating topiramate therapy should have baseline and follow-up urinary calcium/creatinine studies, serum electrolytes, and periodic renal ultrasonography, if the urinary calcium/creatinine ratio increases to a level above normal for age.

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KEYWORDS: hypercalciuria; nephrocalcinosis; nephrolithiasis; topiramate

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Topiramate is an effective drug in treating pediatric patients with refractory partial status epilepticus,¹ infantile spasms,² and other catastrophic epilepsies of infancy.³ Dose-controlled studies show that topiramate can be effectively used as monotherapy for seizures in both children and adults.⁴ Although topiramate causes nephrolithiasis in approximately 1.5% of adults, the frequency of nephrolithiasis or nephrocalcinosis in children receiving long-term topiramate is not completely elucidated.⁵ Shields and Wu⁶ reported 1 case

of nephrolithiasis in 313 children treated for a mean of 722 days with topiramate. A retrospective cross-sectional study of 96 children receiving topiramate therapy identified 5 children (5%) who developed nephrolithiasis on random renal ultrasonography performed between 18 and 33 months of topiramate.⁷ There were no data in this study on nephrocalcinosis or on topiramate dosing or biochemical parameters during topiramate. In addition, Corbin Bush *et al.*⁸ found that 5% of children in a prospective cross-sectional study receiving topiramate for a mean of 27 months developed asymptomatic nephrolithiasis that was found on screening renal ultrasonography. Most of these children had lithogenic abnormalities, such as hypercalciuria, hypocitraturia, and a high urine pH. Finally, clinical kidney stone events occurred in 13 (54%) of 24 nonambulatory and

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neurologically impaired children living in a home for disabled children during topiramate therapy after a mean duration of 36 months.⁹ There were no data on topiramate dosing or biochemical parameters in this study.

Topiramate is similar in structure to acetazolamide, and both drugs inhibit carbonic anhydrase in the renal tubule, although the inhibitory effect of acetazolamide is greater than topiramate.^{10,11} Inhibition of renal tubular carbonic anhydrase has several effects. Metabolic acidosis occurs secondary to impairment of carbonic anhydrase-dependent proximal tubular bicarbonate reabsorption, resulting in increased urinary excretion of bicarbonate.^{12–15} Alkalinizing the urine can lead to calcium phosphate super-saturation and nephrolithiasis. Moreover, inhibition of carbonic anhydrase impairs proximal tubular reabsorption of calcium, leading to increased urinary calcium excretion; this in turn could predispose patients to renal calcium stones or nephrocalcinosis.¹⁶ In addition, metabolic acidosis stimulates proximal tubule reabsorption and metabolism of citrate, leading to hypocitraturia, which is a risk factor for calcium stone formation and nephrocalcinosis.^{16,17} These biochemical mechanisms have been identified in adult patients on topiramate.^{18,19} Indeed, we have previously shown that acetazolamide induces metabolic acidosis and hypercalciuria, leading to nephrocalcinosis and nephrolithiasis in children treated with this drug for post hemorrhagic hydrocephalus.²⁰

Our study, which followed 40 children on topiramate therapy for seizures over an average of 36 months, sought to define the incidence of nephrolithiasis, nephrocalcinosis, or both, as well as the effect that topiramate had on serum bicarbonate (HCO_3) levels and on urinary calcium/creatinine (UCa/Cr) ratios.

METHODS

To analyze the effects of topiramate (Topamax; Ortho-McNeil Neurologic, Titusville, NJ) on UCa/Cr ratios and serum HCO_3 levels, we studied 40 consecutive children ages 11 months to 18 years who started topiramate for seizures between January 1997 and February 2003. Data on the age of initiation of topiramate, type of seizure disorder, duration of topiramate, and concomitant medications were collected. Baseline electrolytes were obtained in all 40 patients before topiramate but only 23 had baseline UCa/Cr ratios before topiramate.

Patients were followed for a mean of 36 months with periodic measurements of serum electrolytes, UCa/Cr ratios, and renal ultrasonography approximately every 6 months, using a 7.5-MHz linear array transducer. All ultrasounds were read blindly by a radiologist skilled in renal ultrasonography. All patients had baseline renal ultrasounds that were normal.

No patients in our study had a previous history of renal disease, parathyroid disease, or rickets. None were concurrently on the carbonic anhydrase inhibitors zonisamide or acetazolamide. Furthermore, during the study period, no patient was on the ketogenic diet, which, like topiramate, induces metabolic acidosis.²¹

Nephrocalcinosis was defined as the presence of hyperechoic medullary pyramids seen in both transverse and longitudinal directions associated with significant corticomedullary echo differentiation. Nephrolithiasis was defined as a distinct echogenic focus with concomitant shadowing.²² A UCa/Cr ratio of 0.21 or greater was used as a cutoff value because prior studies have shown that this level of urinary calcium excretion in children is associated with hematuria, dysuria, urinary urgency, urinary tract infections, and nephrolithiasis.^{23–29} Of the 40 patients, 23 patients had baseline electrolytes and UCa/Cr ratio before the institution of topiramate. Nine of 23 patients had UCa/Cr ratios of 0.21 or greater before topiramate initiation; this group was compared with the 14 patients whose UCa/Cr ratios were normal, and both groups were analyzed for changes in UCa/Cr ratio and serum HCO_3 over time by repeated measures analysis of variance rather than by the Student *t* test. The BMDP program 5V (unbalanced repeated measures analysis of variance) allows for missing measurements at different time periods.³⁰ A maximum likelihood procedure using the Newton-Raphson algorithms was used to obtain estimates of the regression and covariance parameters.³¹ The Wald test was used to test the effects of the treatment group and the length of exposure to topiramate.³² The relationship of UCa/Cr and serum HCO_3 at the time of the maximum topiramate dose in mg/kg was analyzed by linear regression analysis in 25 children who had a UCa/Cr ratio at the time when they were on their maximum dose of topiramate.

Approval was granted for this study by the Institutional Review Board of Baystate Medical Center #03-133. Data were collected in a de-identified manner in compliance with the Health Insurance Portability and Accountability Act of 1996 and our institutional review board.

RESULTS

The seizure types in these 40 children included the following: complex partial seizures ($n = 13$), generalized tonic-clonic ($n = 10$), infantile spasms ($n = 7$), childhood absence ($n = 5$), and Lennox-Gastaut ($n = 5$). The mean age at time of topiramate initiation was 107 months. Only 3 children had a family history of nephrolithiasis and none of the 4 children who later

developed nephrocalcinosis or nephrolithiasis had a family history of kidney stones. Ten children had a gastric tube and 9 did not ambulate and were immobile. Twelve children were on monotherapy with topiramate and 28 children received 1 or 2 additional drugs, including valproic acid ($n = 8$), levetiracetam ($n = 11$), lamotrigine ($n = 9$), or phenobarbital ($n = 2$). No children in the study received zonisamide.

Changes in urinary calcium excretion (UCa/Cr) and serum HCO_3 levels in all 40 patients are presented in Figures 1 and 2. The UCa/Cr ratio increased 2-fold after 6 months of topiramate and there was a significant increase in mean UCa/Cr ratio after 30 months for all 40 patients, which was sustained after 54 months of topiramate therapy ($P < 0.001$). The serum HCO_3 decreased significantly after 6 months of topiramate (Figure 2) and the decrease persisted for up to 60 months of therapy ($P < 0.001$). Nine of 23 children, who had pretreatment urinary determinations, had UCa/Cr ratios of 0.21 or greater before receiving topiramate. The mean age of these children was 36 months (range 7–123 months) and there were 4 girls and 5 boys. Their mean UCa/Cr ratio before topiramate was 0.35 ± 0.11 . Fourteen children had UCa/Cr ratios < 0.21 before topiramate and their mean age was 137 months (range 2–212 months), with 2 girls and 12 boys. Their mean UCa/Cr ratio was 0.07 ± 0.05 . The mean age and mean UCa/Cr ratio was statistically different between the 2 groups ($P < 0.05$). There was no difference between these 2 groups in causes for seizures, family history of nephrolithiasis, gastric tube, or immobilization.

Four children developed renal complications from topiramate, including 2 with nephrolithiasis and 2 who developed renal medullary nephrocalcinosis detected on ultrasound (Table 1). Patient 1 developed clinically significant nephrolithiasis and passed 1 kidney stone after 45 months of topiramate. His renal ultrasound 1 year before this episode showed no nephrolithiasis or

nephrocalcinosis. His marked hypercalciuria during topiramate treatment resolved completely after drug discontinuation. He had a normal renal ultrasound 3 years later and, 5 years after topiramate discontinuation, showed no recurrence of nephrolithiasis. Patient 4 developed two 5-mm renal stones in the right kidney after 60 months of topiramate. His renal ultrasound 12 months before demonstrated no nephrolithiasis or nephrocalcinosis. These 2 stones gradually resolved after topiramate discontinuation and 18 months of potassium citrate. A renal ultrasound 2 years off topiramate showed complete resolution of both stones. Patient 2 developed medullary nephrocalcinosis demonstrated on renal ultrasound after 30 months of topiramate, which resolved off topiramate and without any other therapy after 9 months. Patient 3 developed ultrasound evidence of medullary nephrocalcinosis, which was no longer evident 6 months after discontinuation of topiramate. Three of these 4 children had baseline UCa/Cr ratios in the range of 0.21 to 0.49 before topiramate treatment. All 4 children had significantly higher UCa/Cr ratios and decreased serum HCO_3 during topiramate, which improved once the drug was stopped (Table 1). All 4 children had a serum HCO_3 level below the normal range at the time of diagnosis of nephrolithiasis or nephrocalcinosis while on topiramate. Patients 1 and 4 had low urinary citrate-to-creatinine ratios during topiramate at 0.15 and 0.23, respectively (normal > 0.5). In addition, all 4 children with these complications received long-term topiramate for 30 to 60 months before complications were identified, and none had a family history of nephrolithiasis.

The 9 children with UCa/Cr ratios of ≥ 0.21 before topiramate were compared with the 14 children with normal calcium excretion before topiramate (Figures 3 and 4). There was a greater increase in UCa/Cr ratio while on topiramate in the children who had elevated UCa/Cr ratios before starting topiramate

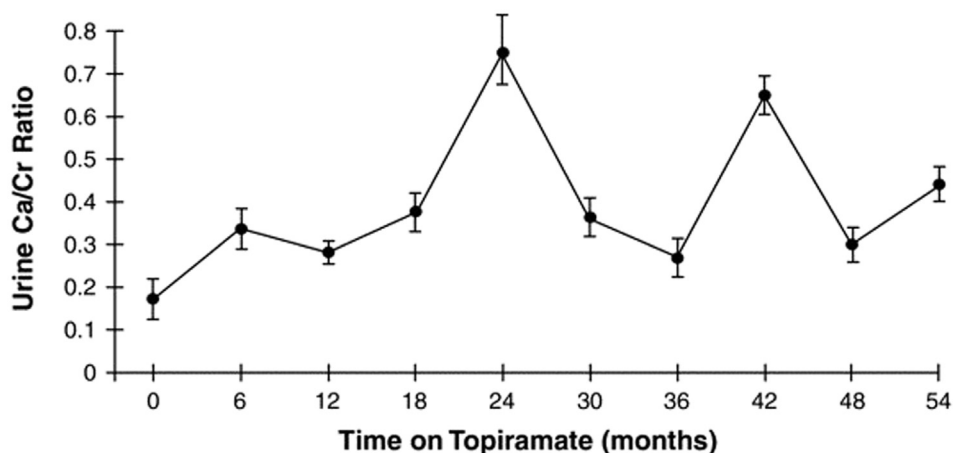


Figure 1. Effects of topiramate on mean \pm SE urinary calcium (Ca)/creatinine (Cr) ratios over time in all 40 patients, $P < 0.001$.

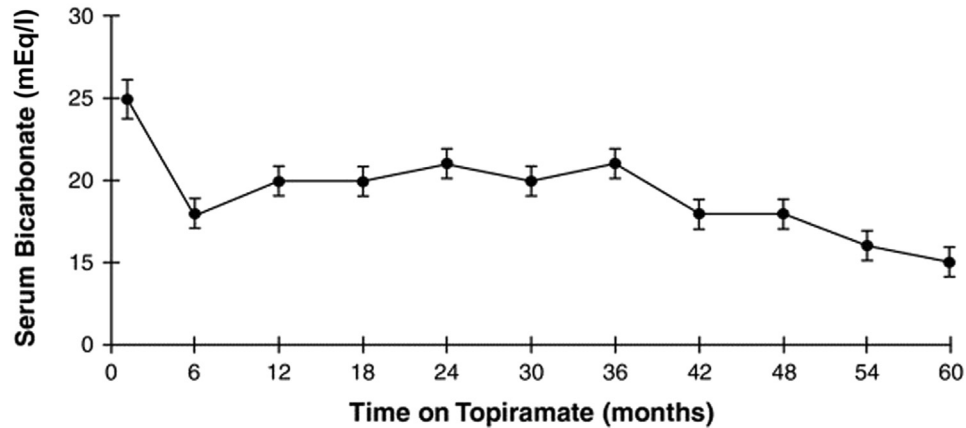


Figure 2. Effects of topiramate on mean \pm SE serum bicarbonate levels over time in all 40 patients, $P < 0.001$.

therapy ($P < 0.001$) compared with the children with normal calcium excretion (Figure 3). There was a greater decrease in serum HCO_3 levels over time (Figure 4) from topiramate in the children with elevated UCa/Cr ratios before topiramate therapy ($P < 0.05$).

There was a significant correlation between the maximum topiramate dose (mg/kg) and urine calcium excretion measured as UCa/Cr ratio in the 25 children who had UCa/Cr ratios definitively measured at the maximum dose of topiramate. The maximum dose range of topiramate therapy was 2.2 to 21.4 mg/kg and the UCa/Cr ranged from 0.03 to 1.0. The r value for this correlation was 0.49 ($P = 0.039$). In addition, there was a significant inverse correlation between the maximum topiramate dose (mg/kg) and serum HCO_3 levels. The range of serum HCO_3 levels was 13 to 27 mEq/L. The r value for this correlation was -0.57 ($P < 0.01$).

DISCUSSION

This study was initiated because of several authors' prior experience using acetazolamide, which, like topiramate, inhibits carbonic anhydrase and induces nephrocalcinosis in children receiving this drug for seizures.²⁰ In the months following the approval of topiramate by the US Food and Drug Administration, our standard of care included surveillance of serum electrolytes, UCa/Cr ratios, and a renal ultrasound every 6 to 12 months.

Our study suggests that long-term topiramate, particularly in young children, can lead to either nephrolithiasis or nephrocalcinosis. In addition, increased urinary calcium excretion found frequently in young children can be worsened by chronic topiramate therapy and the increased calcium excretion persists for up to 5 years during topiramate therapy.

In addition, the decrease in serum HCO_3 was greater in the children with baseline high urinary calcium excretion compared with the healthy control children. Greater systemic acidosis from the carbonic anhydrase inhibitory effect of topiramate could lead to hypercalciuria due to bone buffering of chronic metabolic acidosis. In addition, carbonic anhydrase inhibition may impair proximal tubular calcium reabsorption leading to hypercalciuria, which enhances the risk for nephrocalcinosis or urinary calcium phosphate stones that can have enhanced growth in a more alkaline urinary milieu.

Moreover, carbonic anhydrase II is integral in alpha intercalated cells in cortical and medullary collecting tubules in supplying hydrogen ions to the H^+ -ATPase proton pump. Inhibition of carbonic anhydrase in the distal nephron could lead to impaired distal acidification, and renal tubular acidosis may be caused by topiramate.^{13–15} We did not perform any studies of distal urinary acidification to confirm this hypothesis. We also demonstrated that higher doses of topiramate are associated with increased urinary calcium excretion and lower serum bicarbonate levels.

Table 1. Characteristics of children who developed nephrocalcinosis (NC) or nephrolithiasis (NL) on topiramate (TPM)

Case	Male/Female	NC or NL	Seizure type	Age at TPM initiation, mo	Duration of TPM, mo	UCa/Cr before TPM	UCa/Cr on TPM	UCa/Cr off TPM	Serum HCO_3 before TPM	Serum HCO_3 on TPM, mEq/L	Serum HCO_3 off TPM, mEq/L
1	M	NL	Infant spasms	19	45	0.49	0.95	0.08	24	20	24
2	F	NC	Complex partial seizures	11	30	0.39	1.0	0.08	24	19	22
3	M	NC	Infant spasms	70	58	0.21	0.44	0.25	25	21	24
4	M	NL	Complex partial seizures	24	60	NA	0.52	0.18	26	17	27

UCa/Cr , urinary calcium/creatinine ratio.

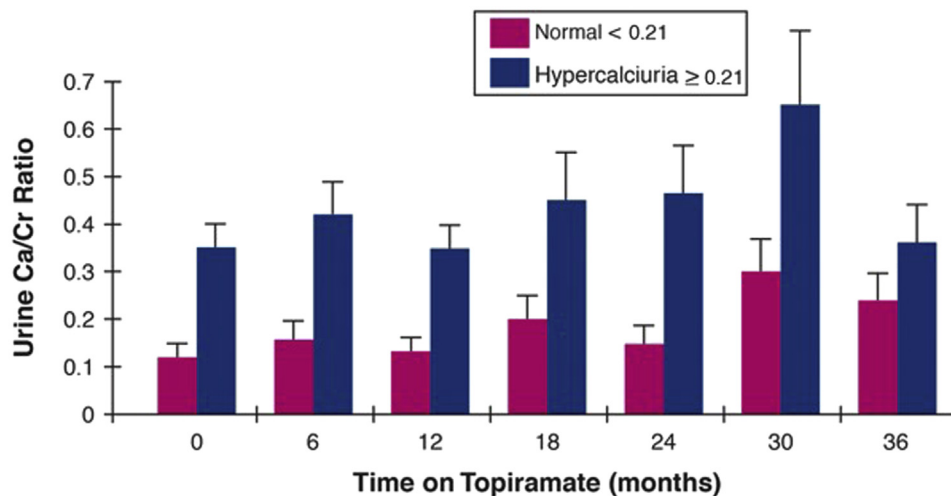


Figure 3. Effects of topiramate on mean \pm SE urinary calcium (Ca)/creatinine (Cr) ratios over time in children with baseline hypercalciuria versus children with normal calcium/creatinine ratios before topiramate, $P < 0.001$.

Children have unique renal physiology that may predispose them to nephrocalcinosis or nephrolithiasis during topiramate therapy. There is an inverse relationship between a child's age and the UCa/Cr ratio: a child younger than 1 year has a mean UCa/Cr level of <0.8 mg/mg, whereas a child older than 5 years can be expected to have an "adult" value of <0.21 mg/mg.^{23,24} However, children with a UCa/Cr ratio >0.21 are at risk for developing gross hematuria, dysuria, urinary urgency, urinary tract infections, and nephrolithiasis.^{25–29} Hypercalciuria is an important predisposing factor in the development of renal calcium deposition; thus, younger children may be at higher risk for the adverse renal side effects of topiramate. We analyzed our patients using a UCa/Cr ratio of less than or greater than 0.21 because of the potential complications of this level of urinary calcium excretion. Indeed, in the only other cross-sectional

study of children receiving topiramate for a mean of 27 months, 5% had hypercalciuria defined as calcium/creatinine >0.20 for children older than 12 months or >0.6 for children aged ≤ 12 months. Ninety-three percent had hypocitraturia defined as a citrate/creatinine ratio <0.5 .⁸ In this study, there was no correlation of topiramate dose to the urinary calcium excretion, but the relationship of maximum topiramate dose was not analyzed.

The long-term renal effects of nephrocalcinosis are unknown, but studies in premature infants who develop this complication during the neonatal period have shown permanent reduction in glomerular filtration rate in half the children tested 3 to 7 years later.^{33,34} In our 2 patients with nephrocalcinosis, this condition gradually resolved during serial ultrasounds obtained after stopping topiramate, but detailed measurements of

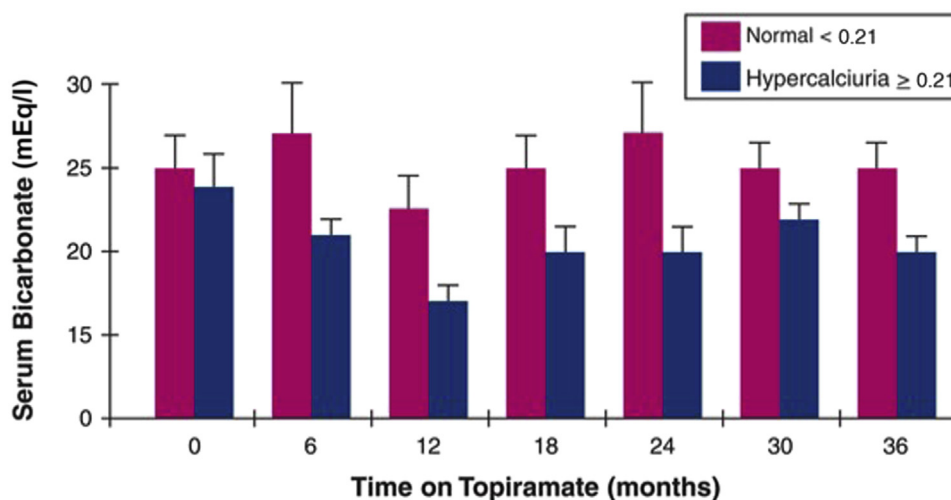


Figure 4. Effects of topiramate on mean \pm SE serum bicarbonate over time in children with baseline hypercalciuria versus children with normal calcium/creatinine ratios before topiramate, $P < 0.05$.

glomerular filtration rate were not performed. Even before frank stones are formed, nephrocalcinosis can develop, which can lead to impaired renal function. Because these conditions can be clinically silent, there is the possibility that painless renal damage could go undetected. Our study underscores the importance of titrating the dose of topiramate to the lowest effective dose to control seizures to lessen the impact of this drug on urinary calcium excretion.

The potential negative impact on bone growth and mineralization in children during drug topiramate therapy has not been studied. Children who have higher-than-usual losses of calcium due to hypercalciuria may have less skeletal calcium accretion, particularly when the dietary intake of calcium is low and sodium is high.^{35,36} Studies of the potential impact of hypercalciuria on children's bone development during topiramate are needed.

Limitations of our study include serum electrolytes and UCa/Cr ratios in only 23 of 40 patients before the initiation of topiramate therapy. In addition, the follow-up urinary data were incomplete at some of the 6-month intervals, making it more difficult to establish a more significant relationship of sustained topiramate therapy on urinary calcium excretion.

Before starting topiramate, we recommend baseline evaluation with a urinalysis, UCa/Cr ratio, and serum electrolytes. It also may be useful to measure urinary citrate/creatinine ratio, but this recommendation must await confirmation by additional longitudinal studies in children treated with topiramate. All children, regardless of their initial levels, should have serum electrolytes and UCa/Cr followed at 6-month intervals. For those children found to have baseline hypercalciuria, as defined as a calcium/creatinine ratio >0.21 we recommend renal ultrasounds at the initiation of topiramate and every 6 months to a year thereafter. Renal ultrasonography is safe and inexpensive, and it is preferable to standard plain film radiography for early detection of nephrocalcinosis.³⁷ Grading scales for nephrocalcinosis are available to enhance intra- and interobserver reliability.³⁸ Although computed tomography scans are more sensitive than ultrasonography in detecting nephrocalcinosis, the increased cost and radiation exposure are not justified and await further studies in children on topiramate therapy.

For those children who have hypercalciuria either at baseline or while on topiramate drug therapy, and for those children who develop decreased serum HCO_3^- levels, potassium citrate therapy may be useful to prevent nephrolithiasis or nephrocalcinosis. By providing anionic substrates that bind calcium ions, potassium citrate can prevent urinary calcium phosphate and oxalate stone formation by increasing

urinary citrate; however, it also alkalinizes the urine, making it more conducive to calcium phosphate crystallization. Potassium citrate, instead of sodium citrate, is the preferred preparation, because increased sodium intake in the medication could lead to increases in urinary calcium excretion. When potassium citrate is dosed at 2 to 3 mEq/kg per day, it effectively decreases the UCa/Cr ratio in children with renal stones.^{39,40} Further studies are needed of potassium citrate therapy in children receiving topiramate. Our study is limited by the lack of urinary pH and urinary citrate/creatinine ratios measured longitudinally.

CONCLUSION

Significant renal complications occurred in 10% (4/40) of this cohort of pediatric patients on topiramate: both nephrocalcinosis and nephrolithiasis were observed. A significant decrease in serum HCO_3^- levels occur with prolonged topiramate therapy, consistent with its inhibitory effect on carbonic anhydrase. Because topiramate increases urinary calcium excretion, it must be used with care, particularly in the youngest patients whose baseline UCa/Cr ratios are highest.

We recommend that all children initiating topiramate therapy should have baseline UCa/Cr studies and serum electrolytes, which are measured approximately every 6 months during topiramate therapy. In children younger than 2 years and in children with UCa/Cr above normal for age, renal ultrasonography is indicated at 6-month intervals. Topiramate therapy should be withdrawn in children who develop nephrolithiasis or nephrocalcinosis with a high chance of resolution of these disorders. The long-term effects of these complications during topiramate are unknown.

DISCLOSURE

All the authors declared no competing interests.

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