Published in final edited form as:

Epilepsy Res. 2010 June ; 90(1-2): 151–156. doi:10.1016/j.epilepsyres.2010.04.005.

Urolithiasis on the ketogenic diet with concurrent topiramate or zonisamide therapy

Elahna Paul^{a,*}, Kerry D. Conant^b, Irie E. Dunne^b, Heidi H. Pfeifer^b, David A. Lyczkowski^b, Michael A. Linshaw^a, and Elizabeth A. Thiele^b

^a Pediatric Nephrology Unit, Massachusetts General Hospital, Boston, MA, USA

^b Pediatric Epilepsy Program and Ketogenic Diet Clinic, Departments of Neurology and Pediatrics, Massachusetts General Hospital, Boston, MA, USA

Summary

Children with refractory epilepsy who are co-treated with the ketogenic diet (KD) and carbonic anhydrase inhibitor (CA-I) anti-epileptic medications including topiramate (TPM) and zonisamide (ZNS) are at risk for urolithiasis. Retrospective chart review of all children treated with ketogenic therapy at our institution was performed in order to estimate the minimal risk of developing signs or symptoms of stone disease. Children ($N = 93$) were classified into groups according to KD +/- CA-I co-therapy. Fourteen patients had occult hematuria or worse, including 6 with radiologically confirmed stones. Three of 6 calculi developed in the KD + ZNS group of 17 patients who were co-treated for a cumulative total of 97 months (3.1 stones per 100 patient months). One confirmed stone was in the KD + TPM group of 22 children who were co-treated for a cumulative total of 263 months (0.4 stones per 100 patient months). All six patients had at least three of five biochemical risk factors including metabolic acidosis, concentrated urine, acid urine, hypercalciuria and hypocitraturia. Standard of care interventions to minimize hypercalciuria, crystalluria and stone formation used routinely by pediatric nephrologists should also be prescribed by neurologists treating patients with combination anti-epileptic therapy. Non-fasting KD initiation, fluid liberalization, potassium citrate prophylaxis as well as regular laboratory surveillance are indicated in this high risk population.

Keywords

Ketogenic diet; Topiramate; Zonisamide; Kidney stones; Epilepsy

Introduction

The ketogenic diet (KD) is a high-fat, low carbohydrate, protein sufficient diet first used in 1921 to ameliorate refractory epilepsy (reviewed in Freeman et al., 2007). Despite its remarkable efficacy in some individuals, the chronic metabolic acidosis, aciduria, hypercalciuria and hypocitraturia of the KD predispose patients to urolithiasis (Furth et al., 2000). Urinary stone formation is modulated by three inter-related variables: urine salts, urine volume and urine pH. Calcium crystal formation is favored by high concentrations of stone-forming solutes (e.g. calcium, oxalate, phosphate, urate), low concentrations of inhibitors (e.g. citrate, magnesium) and extremes in urine pH. KD-associated acidosis

promotes hypercalciuria partly through bone demineralization, essentially washing boney calcium stores into the urine (reviewed in Wiederkehr and Krapf, 2001) and acidosis also drives renal reabsorption of citrate and bicarbonate to help buffer the acidemia, which in turn generates a maximally acidified, citrate-depleted, calcium-enriched urine that is prone to calcium precipitation. Volume restriction or depletion during acute illness heightens the risk of urolithiasis by concentrating the urine and its stone-forming solutes. Within the past decade, renal calculi have been reported in 1.4—8.7% of children on the KD (Freeman et al., 1998; Hassan et al., 1999; Furth et al., 2000; Maydell et al., 2001; Nordli et al., 2001; Kossoff et al., 2002a,b; Vaisleib et al., 2004; Sampath et al., 2007) and hematuria in as many as 10% (Lyczkowski et al., 2005). In general, lower rates are reported when GU imaging is restricted to patients with pain or macroscopic hematuria, whereas higher rates of urolithiasis are detected when imaging is also performed in cases of occult hematuria or hypercalciuric hypocitraturia. Combined with the pediatric practice preference of screening with renal ultrasound rather than CT scan, it is quite likely that documented rates of KD-associated urolithiasis substantially under-estimate the GU stone burden in this patient population.

Topiramate (TPM), zonisamide (ZNS) and acetazolamide (AZM)—anti-epileptic drugs (AEDs) with carbonic anhydrase inhibitor (CA-I) activity—also predispose to urinary crystal formation by interfering with acid-base homeostasis and with renal sodium and water handling (Futagi et al., 1996; Inoue et al., 2000; Takeoka et al., 2001; Philippi et al., 2002; Sheth, 2004; Garriss and Oles, 2005; Groeper and McCann, 2005; Warner et al., 2008; Goyal et al., 2009). CA-inhibiting agents block normal bicarbonate reabsorption which initially alkalinizes the urine and acidifies the blood but eventually acidifies the urine as well. These AEDs can also promote hypercalciuria via sodium and calcium wasting (reviewed in Purkerson and Schwartz, 2007). The renal compensation for metabolic acidosis generates hypocitraturia which further augments the risk of crystalluria (Lamb et al., 2004; Go, 2005; Welch et al., 2006). TPM and ZNS monotherapy have been associated with rates of urolithiasis ranging from 1.5 to 3.7% (Leppik et al., 1993; Shorvon, 1996; Leppik, 1999; Wroe, 2007), whereas the stronger CA-I activity of AZM may account for its substantially higher rate of associated stone disease (reported as high as 15% (Tawil et al., 1993)).

While concurrent use of KD and CA-I anti-epileptic therapy theoretically risk exacerbating rates of urolithiasis beyond either modality alone, we had previously seen no nephrolithiasis in a relatively small sample of 14 patients co-treated with KD + TPM (Takeoka et al., 2002) and others have also reported that the frequency of renal stones in KD patients does not increase with TPM therapy (Kossoff et al., 2002a). Data on KD + ZNS co-therapy, however, are still generally lacking. This current study describes a larger cohort of 93 KD patients treated with or without ZNS, TPM and AZM with attention to urolithiasis and associated risk factors. Review of this retrospective data suggests that TPM and ZNS can be combined with KD therapy without substantially increasing urologic findings. Ketotic patients treated with or without concomitant CA-I anticonvulsants have three main risk factors for calculus formation: hypercalciuria, hypocitraturia and acid urine. In general, a dilute urine with a neutral pH, low calcium and high citrate concentrations are the goals of stone prevention therapies in this population.

Methods

Patient population and chart review

To evaluate the incidence of urolithiasis during KD co-therapy with AZM, TPM and/or ZNS, we retrospectively reviewed the records of children followed at the Ketogenic Diet Clinic of the Massachusetts General Hospital between February 2002 and December 2007.

Ninety-three patients were identified whose KD initiations occurred before 21 years of age and who were compliant for at least 1 month with a caloric ketogenic ratio $\geq 3:1$.

KD induction, maintenance and screening protocols

There was a procedural change in ketosis induction over this study period. KD initiations before May 2003 ($N = 48$) followed a gradual initiation protocol in which one third of estimated daily caloric requirement was consumed on day 1, two thirds on day 2, and full caloric intake on day 3. After May 2003, patients ($N = 45$) began the full-strength diet on day 1 without preparatory fasting. There was no fluid restriction in either group. Before 2002, KD patients were prescribed buffering agents only if they exhibited symptoms of metabolic acidosis (lethargy, nausea, vomiting) or if serum bicarbonate fell below 15 mmol/L. Beginning in 2002, KD patients co-treated with TPM or ZNS were prophylactically treated with sodium citrate or sodium bicarbonate. In 2003, potassium citrate replaced sodium citrate as the buffer of choice to avoid sodium induced hypercalciuria. Beginning in 2005, all KD patients, regardless of pharmacotherapy were buffered prophylactically with a carbohydrate-free formulation of potassium citrate beginning at 2 mEq/kg/day divided TID and adjusted as needed to achieve serum bicarbonate levels ≥ 20 mmol/L and neutral urine pH.

Renal stone disease

Patient urine is screened at least weekly by dipstick for ketones, pH, specific gravity and occult hematuria. Formal urinalysis, quantitative urine chemistries and blood chemistries are screened at least quarterly, and also whenever hematuria or clinical concerns arise. The suspicion of urolithiasis has also evolved over time. Initially, only patients complaining of renal colic and macroscopic hematuria were evaluated radiologically for urolithiasis. Subsequently, even in the absence of firm radiologic confirmation, patients with occult hematuria were also suspected of having stone disease if their hematuria-triggered evaluation revealed biochemical risk factors including metabolic acidosis, extremes of urinary pH (<6.5 or >8.0), hypercalciuria (random urine calcium/creatinine ratios >0.6 in mg/mg for children 6–24 months old and >0.2 for children >2 years) and/or hypocitraturia (urine citrate <400 mg per g creatinine) (Gillespie and Stapleton, 2004). Currently all patients initiating co-therapy with KD and CA-I medication are pre-screened for risk factors predisposing to nephrolithiasis and kidneys are sometimes imaged for pre-existing calculi.

Statistical analysis

Chi-squared analysis and Student's *t*-tests were performed using Microsoft excel. Specific comparisons between patient groups are noted in the text and *p* values >0.05 are reported as not significant in all cases.

Results

Ninety-three pediatric patients who tolerated the KD for at least 1 month were reviewed for this study. The majority of patients ($N = 86$) fall into one of three larger treatment groups summarized in Table 1: KD + ZNS co-therapy ($N = 17$), KD + TPM co-therapy ($N = 22$) and KD-only ($N = 47$). There is no significant difference in gender, age, ketosis induction method (fasting versus non-fasting) nor duration of ketogenic therapy among these three treatment groups by Chi-squared analysis. Nor are there significant differences in group composition of ambulatory versus non-ambulatory children (excluding the 3 who began walking during therapy) nor of tube fed versus orally fed children (excluding the 6 patients who received a combination of both). Similarly, there is no significant difference in age or duration of KD + CA-I co-therapy between the KD + TPM and the KD + ZNS groups by student *t*-test, although 100% of KD + ZNS patients had previously failed a trial of CA-I

monotherapy before initiating the KD and hence may be at increased cumulative risk for stone disease. An additional five of the 93 patients were treated concurrently with KD + TPM + ZNS and another two were co-treated with KD + AZM. These seven children are not included in Table 1.

Nephrolithiasis was confirmed by renal ultrasound or CT scan in six children who presented with non-infectious urologic findings that ranged from painless occult hematuria to symptomatic renal colic. This group of children includes 1 of 22 (4.5%) KD + TPM patients, 3 of 17 (17.6%) KD + ZNS patients, 0 of 47 KD-only patients, 1 KD + TPM + ZNS patient and 1 KD + AZM patient. Their treatment regimens from the initiation of CA-I therapy to the diagnosis of renal stones are depicted in Fig. 1. Each of these urolithiasis patients had at least three of five biochemical risk factors of stone disease (Table 2). Hypercalciuria in 24-h urine collections and/or random urine samples (defined as calcium excretion of >4 mg/kg/day and/or calcium/creatinine ratios >0.6 mg/mg in children 6–24 months old and >0.2 mg/mg in children >2 years) was noted in all six children. Hypocitraturia (defined as <400 mg citrate/g creatinine) was seen in the four who were tested (two in random samples and two via 24 h collection). Acid urine with $\text{pH} \leq 6.0$ was seen in four of the children and concentrated urine specific gravity values >1.025 in two. Five of the six had metabolic acidosis with serum bicarbonate ≤ 20 mmol/L.

Painless occult hematuria was observed in an additional eight children without concomitant detection of urinary calculi: 2 of 22 (9.0%) KD + TPM patients, 1 of 17 (5.8%) KD + ZNS patients and 5 of 47 (10.6%) KD-only patients. In general, these children had fewer biochemical risk factors than those in whom stones were found (Table 2).

When the KD + ZNS and KD + TPM co-therapy groups were analyzed alone and also when combined as a larger KD + CA-I group of 39 children, no significant differences were noted by student t-test between the children with ($N = 7$) and without ($N = 32$) urologic findings in terms of gender, age, duration of co-therapy, ambulatory status, oral versus tube feed status or KD induction protocol. None of the patients discontinued KD treatment because of urolithiasis.

Discussion

Ninety-three pediatric patients who tolerated the KD for at least 1 month were reviewed for this retrospective study. Two of the 93 patients were treated concurrently with KD + AZM and another five were co-treated with KD + TPM + ZNS. Of the remaining KD patients summarized in Table 1, 17 were co-treated with ZNS and 22 with TPM. In this cohort of 86 KD patients treated with and without CA inhibitors, KD + ZNS co-therapy but not KD + TPM co-therapy was associated with an elevated rate of nephrolithiasis over the KD-alone ($p = 0.003$ and 0.14 , respectively; Table 1). Calculi were documented almost four times more often in KD + ZNS patients (17.6%) than in KD + TPM children (4.5%), and never in KD-only regimens. Although not statistically significant, similar trends are seen when including the hematuria cases where stones were suspected but not radiologically confirmed. When duration of exposure is considered, stones are seven-fold more common in the KD + ZNS versus KD + TPM groups (3.1 versus 0.4 stones per 100 patient months, respectively). Variations in pre-KD exposure to CA-I agents may contribute to these observations. Many of the children co-treated with KD + ZNS for example, had failed ZNS monotherapy as well as prior treatment with TPM. It is plausible that their cumulative albeit sequential exposure to these agents augmented their risk of nephrolithiasis.

Our findings differ in a number of respects from older patient cohorts. A 2002 study of 301 ketotic children (74 co-treated with KD + TPM, 6 with KD + ZNS and 221 on KD-alone)

reported equivalent rates of urolithiasis in all KD + CA-I patients versus KD-only patients (6.7% and 6.3%, respectively; (Kossoff et al., 2002a)). Moreover, there were no renal calculi among their limited number of patients co-treated with KD + ZNS. The higher rates of KD-associated nephrolithiasis in the older study compared to the present report may be attributable, in part, to an evolution in KD induction and maintenance protocols. In particular, fluid restriction and pre-induction fasting have been eliminated from our protocol. Fluid intake adequate to maintain urine diluted to a specific gravity <1.010 helps protect against urolithiasis. Although theoretically simple, this maneuver demands more compliance than most pediatric patients are able to muster so that ancillary measures are needed to reduce urinary stone-forming solutes, to increase crystallization inhibitors and to neutralize serum and urine pH.

Our KD patients now routinely receive buffering agents for stone prophylaxis. Both citrate and bicarbonate can correct the metabolic acidosis of KD and CA-I treated patients. In addition to its buffering activity, citrate also doubles as an inhibitor of crystal formation when it passes into the urine and chelates urinary calcium. Not only is citrate preferable to bicarbonate as an oral buffering agent, but also potassium citrate is unequivocally superior to sodium citrate in patients at risk for calcium stone disease, primarily because sodium loads promote hypercalciuria (reviewed in Srivastava and Alon, 2007). Equivalent doses of sodium and potassium citrate supplements increase citraturia to a similar extent, but only potassium citrate simultaneously reduces calciuria (Sakhaee et al., 1983; Preminger et al., 1988). In other words, when kidneys clear an oral sodium load such as sodium bicarbonate or sodium citrate, they also increase urinary calcium excretion and thus increase the risk for urolithiasis. Conversely, excess potassium is excreted in exchange for urinary sodium and calcium, thereby mitigating the hypercalciuric effects of ketosis and CA inhibition. Despite concerns of hypercalciuria, it is important to explicitly counsel families NOT to limit dietary calcium intake. Although calcium restriction might help reduce calciuria, inadequate dietary calcium increases gut absorption of oxalate, thereby increasing renal oxalate excretion and potentiating oxalate stone formation. Inadequate dietary calcium also promotes calcium mobilization from bone, potentially exacerbating KD-associated osteomalacia or osteoporosis.

Of our six stone patients, it is perhaps instructive that the three who developed stones within only days to weeks of KD initiation (patients 1, 3 and 4) underwent ketosis induction before we routinely prescribed buffering agents (Fig. 1). Similarly, the other three patients with calculi had received sodium rather than potassium salts, evidently at doses too low to neutralize their urine pH and/or normalize their serum bicarbonate while simultaneously exacerbating their hypercalciuria (Table 2). These observations support our contention that potassium citrate should be used routinely in ketotic patients, as also proposed in a previous report (McNally et al., 2009), particularly in conjunction with anti-epileptic CA-I co-therapy.

Summary

Although KD treatment, AZM, TPM, and ZNS monotherapy all predispose to nephrolithiasis, the increased risk from co-therapy with each of the CA-I agents is not equal. Our experience suggests that calculi are more frequent in patients receiving KD + ZNS co-therapy rather than KD + TPM or KD-alone ($p = 0.003$ and 0.14 , respectively). Although the reasons for these differences are obscure, it is well recognized that urolithiasis develops in the presence of metabolic acidosis, acid urine, hypercalciuria and hypocitraturia. Adequate hydration with brisk urine output is an absolute requirement for stone prophylaxis. Buffering with sodium bicarbonate, sodium citrate or potassium citrate can correct acidosis, but potassium citrate is the agent of choice because it also increases urinary citrate and helps

reduce calciuria. Hypercalciuric patients with hematuria or discomfort should be treated for urolithiasis even in absence of positive imaging studies, and referral to a pediatric nephrologist or urologist is indicated. Careful medical management of asymptomatic hypercalciuric patients on the KD with or without concomitant CA-I therapy will minimize the risk of progressive stone disease. Serial review of urine calcium, creatinine and citrate in addition to urinalysis for pH, specific gravity and occult hematuria should be standard of care in epilepsy patients at risk for urolithiasis.

References

- Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. *Pediatrics*. 1998; 102:1358–1363. [PubMed: 9832569]
- Freeman JM, Kossoff EH, Hartman AL. The ketogenic diet: one decade later. *Pediatrics*. 2007; 119:535–543. [PubMed: 17332207]
- Furth SL, Casey JC, Pyzik PL, Neu AM, Docimo SG, Vining EP, Freeman JM, Fivush BA. Risk factors for urolithiasis in children on the ketogenic diet. *Pediatr. Nephrol.* 2000; 15:125–128. [PubMed: 11095028]
- Futagi Y, Otani K, Abe J. Growth suppression in children receiving acetazolamide with antiepileptic drugs. *Pediatr. Neurol.* 1996; 15:323–326. [PubMed: 8972532]
- Garris SS, Oles KS. Impact of topiramate on serum bicarbonate concentrations in adults. *Ann. Pharmacother.* 2005; 39:424–426. [PubMed: 15701764]
- Gillespie RS, Stapleton FB. Nephrolithiasis in children. *Pediatr. Rev.* 2004; 25:131–139. [PubMed: 15060181]
- Go T. Effect of antiepileptic drug polytherapy on crystalluria. *Pediatr. Neurol.* 2005; 32:113–115. [PubMed: 15664771]
- Goyal M, Grossberg RI, O'Riordan MA, Davis ID. Urolithiasis with topiramate in nonambulatory children and young adults. *Pediatr. Neurol.* 2009; 40:289–294. [PubMed: 19302942]
- Groeper K, McCann ME. Topiramate and metabolic acidosis: a case series and review of the literature. *Paediatr. Anaesth.* 2005; 15:167–170. [PubMed: 15675937]
- Hassan AM, Keene DL, Whiting SE, Jacob PJ, Champagne JR, Humphreys P. Ketogenic diet in the treatment of refractory epilepsy in childhood. *Pediatr. Neurol.* 1999; 21:548–552. [PubMed: 10465141]
- Inoue T, Kira R, Kaku Y, Ikeda K, Gondo K, Hara T. Renal tubular acidosis associated with zonisamide therapy. *Epilepsia*. 2000; 41:1642–1644. [PubMed: 11114225]
- Kossoff EH, Pyzik PL, Furth SL, Hladky HD, Freeman JM, Vining EP. Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. *Epilepsia*. 2002a; 43:1168–1171. [PubMed: 12366731]
- Kossoff EH, Pyzik PL, McGrogan JR, Vining EP, Freeman JM. Efficacy of the ketogenic diet for infantile spasms. *Pediatrics*. 2002b; 109:780–783. [PubMed: 11986436]
- Lamb EJ, Stevens PE, Nashef L. Topiramate increases biochemical risk of nephrolithiasis. *Ann. Clin. Biochem.* 2004; 41:166–169. [PubMed: 15025812]
- Leppik IE, Willmore LJ, Homan RW, Fromm G, Oommen KJ, Penry JK, Sackellares JC, Smith DB, Lesser RP, Wallace JD, et al. Efficacy and safety of zonisamide: results of a multicenter study. *Epilepsy Res.* 1993; 14:165–173. [PubMed: 8453952]
- Leppik IE. Zonisamide. *Epilepsia*. 1999; 40(Suppl. 5):S23–29. [PubMed: 10530691]
- Lyczkowski DA, Pfeifer HH, Ghosh S, Thiele EA. Safety and tolerability of the ketogenic diet in pediatric epilepsy: effects of valproate combination therapy. *Epilepsia*. 2005; 46:1533–1538. [PubMed: 16146450]
- Maydell BV, Wyllie E, Akhtar N, Kotagal P, Powaski K, Cook K, Weinstock A, Rothner AD. Efficacy of the ketogenic diet in focal versus generalized seizures. *Pediatr. Neurol.* 2001; 25:208–212. [PubMed: 11587874]

- McNally MA, Pyzik PL, Rubenstein JE, Hamdy RF, Kossoff EH. Empiric use of potassium citrate reduces kidney-stone incidence with the ketogenic diet. *Pediatrics*. 2009; 124:e300–304. [PubMed: 19596731]
- Nordli DR Jr, Kuroda MM, Carroll J, Koenigsberger DY, Hirsch LJ, Bruner HJ, Seidel WT, De Vivo DC. Experience with the ketogenic diet in infants. *Pediatrics*. 2001; 108:129–133. [PubMed: 11433065]
- Philippi H, Boor R, Reitter B. Topiramate and metabolic acidosis in infants and toddlers. *Epilepsia*. 2002; 43:744–747. [PubMed: 12102678]
- Preminger GM, Sakhaee K, Pak CY. Alkali action on the urinary crystallization of calcium salts: contrasting responses to sodium citrate and potassium citrate. *J. Urol*. 1988; 139:240–242. [PubMed: 3339718]
- Purkerson JM, Schwartz GJ. The role of carbonic anhydrases in renal physiology. *Kidney Int*. 2007; 71:103–115. [PubMed: 17164835]
- Sakhaee K, Nicar M, Hill K, Pak CY. Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. *Kidney Int*. 1983; 24:348–352. [PubMed: 6645208]
- Sampath A, Kossoff EH, Furth SL, Pyzik PL, Vining EP. Kidney stones and the ketogenic diet: risk factors and prevention. *J. Child. Neurol*. 2007; 22:375–378. [PubMed: 17621514]
- Sheth RD. Metabolic concerns associated with antiepileptic medications. *Neurology*. 2004; 63:S24–29. [PubMed: 15557547]
- Shorvon SD. Safety of topiramate: adverse events and relationships to dosing. *Epilepsia*. 1996; 37(Suppl. 2):S18–S22. [PubMed: 8641242]
- Srivastava T, Alon US. Pathophysiology of hypercalciuria in children. *Pediatr. Nephrol*. 2007; 22:1659–1673. [PubMed: 17464515]
- Takeoka M, Holmes GL, Thiele E, Bourgeois BF, Helmers SL, Duffy FH, Riviello JJ. Topiramate and metabolic acidosis in pediatric epilepsy. *Epilepsia*. 2001; 42:387–392. [PubMed: 11442157]
- Takeoka M, Riviello JJ Jr, Pfeifer H, Thiele EA. Concomitant treatment with topiramate and ketogenic diet in pediatric epilepsy. *Epilepsia*. 2002; 43:1072–1075. [PubMed: 12199733]
- Tawil R, Moxley RT 3rd, Griggs RC. Acetazolamide-induced nephrolithiasis: implications for treatment of neuromuscular disorders. *Neurology*. 1993; 43:1105–1106. [PubMed: 8170551]
- Vaisleib II, Buchhalter JR, Zupanc ML. Ketogenic diet: outpatient initiation, without fluid, or caloric restrictions. *Pediatr. Neurol*. 2004; 31:198–202. [PubMed: 15351019]
- Warner BW, LaGrange CA, Tucker T, Bensalem-Owen M, Pais VM Jr. Induction of progressive profound hypocitraturia with increasing doses of topiramate. *Urology*. 2008; 72:29–32. discussion 32–23. [PubMed: 18436283]
- Welch BJ, Graybeal D, Moe OW, Maalouf NM, Sakhaee K. Biochemical and stone-risk profiles with topiramate treatment. *Am. J. Kidney Dis*. 2006; 48:555–563. [PubMed: 16997051]
- Wiederkehr M, Krapf R. Metabolic and endocrine effects of metabolic acidosis in humans. *Swiss Med. Wkly*. 2001; 131:127–132. [PubMed: 11416968]
- Wroe S. Zonisamide and renal calculi in patients with epilepsy: how big an issue? *Curr. Med. Res. Opin*. 2007; 23:1765–1773. [PubMed: 17594758]

Figure 1.

Urolithiasis precipitated by anti-epileptic therapy in six KD patients. Therapeutic regimens for each of six patients listed on the y-axis are displayed graphically from the initiation of CA-I monotherapy at 0 month on the x-axis, until signs or symptoms of a calculus were noted in each patient. Each anti-epileptic agent is represented by a different colored bar, and co-therapy occurred whenever bars appear to overlap. Renal colic (RC), macroscopic hematuria (MH) and occult hematuria (OH) occurred anywhere from 1 day to 7 months after induction of ketosis.

Table 1Characteristics of KD patients with and without urolithiasis ($N = 86$).

Treatment groups (N)	KD + ZNS (17)	KD + TPM (22)	KD-only (47)
Female patients (%)	7 (41%)	7 (32%)	25 (53%)
Non-ambulatory patients (%)	7 (41%)	9 (43%)	12 (27%)
Exclusively tube fed patients (%)	3 (21%)	8 (36%)	9 (21%)
Pre-KD CA-I exposure (%)	17 (100%) [*]	18 (82%)	31 (66%)
Pre-KD fasting (%)	8 (47%)	10 (45%)	23 (49%)
KD start age (mean years $\pm$ SD)	5.7 $\pm$ 3.4	4.8 $\pm$ 3.9	6.5 $\pm$ 4.8
KD duration (mean months $\pm$ SD)	28 $\pm$ 28	26 $\pm$ 21	23 $\pm$ 20
KD total patient, months	478	561	1068
Co-Rx start age (mean years $\pm$ SD)	5.9 $\pm$ 3.3	5.3 $\pm$ 3.9	–
Co-Rx duration (mean months $\pm$ SD)	6 $\pm$ 6	12 $\pm$ 18	–
Co-Rx total patient, months	97	263	–
Number with hematuria only (%)	1 (5.9%)	2 (9.1%)	5 (10.6%)
Number with urolithiasis (%)	3 (17.6%) ^{**}	1 (4.5%)	0
Urolithiasis per 100 months of co-Rx	3.1	0.4	–

^{*} There is a significant difference in pre-ketosis exposure to CA-I medication (either TPM or AZM) between the KD + ZNS and KD-only groups ($p = 0.01$ by Chi-squared analysis).

^{**} There is a significant difference in confirmed urolithiasis between the KD + ZNS and KD-only groups ($p = 0.003$ by Chi-squared analysis).

Table 2

KD patients with urologic signs or symptoms.

Pt	Sex	CA-1 agent		KD ^a		Ketosis ratio	β -OH butyrate	Buffering agent	Urolithiasis ^b		Biochemical risk factors ^c				
		ZNS	TPM	AZM	Start age				Time to urologic finding	Urologic finding	Calculus seen	Serum bicarb	SG	pH	Citrate
1	M	+	+	-	6 years 2 months	3.5:1	3.8	None	1 day	OH	Y	15	1.015	6.0	1.5
2	M	+	-	-	3 years 1 months	4:1	6.3	KCitrates	3 weeks	OH	N	17	-	-	-
3	M	+	-	-	9 years 2 months	3.5:1	5.0	None	4 weeks	OH→RC	Y	13	1.019	6.0	0.4
4	F	+	-	-	3 years 5 months	4:1	6.7	none	6 weeks	OH	Y	22	1.028	5.5	0.9
5	F	+	-	-	4 years 8 months	2.5:1	5.5	NaBicarb	6 months	OH→MH	Y	20	1.015	6.5	0.3
6	F	-	+	-	6 years 6 months	4:1	5.5	KCitrates	1 day	OH	N	22	1.026	6.0	-
7	M	-	+	-	0 years 8 months	4:1	-	KCitrates	6 months	OH	N	21	1.015	7.5	2.0
8	M	-	+	-	1 years 6 months	4:1	5.5	NaCitrates	6 months	MH	Y	20	1.029	6.0	1.0
9	M	-	-	+	7 years 5 months	4:1	-	NaCitrates	7 months	MH→RC	Y	16	1.020	6.5	0.6
10	F	-	-	-	2 years 11 months	3.75:1	3.6	KCitrates	1 day	OH	N	20	1.025	6.0	-
11	F	-	-	-	3 years 0 months	3.5:1	6.7	NaBicarb	5 months	OH	N	21	1.010	5.0	0.1
12	F	-	-	-	6 years 1 months	4:1	9.2	None	13 months	OH	N	18	1.030	5.0	-
13	F	-	-	-	9 years 10 months	4:1	7.1	KCitrates	13 months	OH	N	23	1.031	6.0	0.5
14	M	-	-	-	3 years 8 months	4:1	5.3	None	4.5 years	OH	N	23	1.029	6.0	-

^aNone of these patients underwent intensification of ketosis therapy after KD induction was completed. β -OH butyrate: beta-hydroxybutyrate (mmol/L).

^bPresenting signs and symptoms include occult hematuria (OH), macroscopic hematuria (MH) and renal colic (RC); an arrow indicates progression.

^c Biochemical risk factors include serum bicarbonate (mmol/L), urine specific gravity, urine pH, urine calcium/creatinine ratio (mg/mg) and urine citrate/creatinine ratio (mg/g).