

## Topiramate-Induced Nephrolithiasis

RAMSAY L. KUO, M.D.,<sup>1</sup> MICHAEL E. MORAN, M.D.,<sup>2</sup> DENNIS H. KIM, M.D.,<sup>2</sup>  
HARRISON M. ABRAHAMS, M.D.,<sup>2</sup> MARK D. WHITE, M.D.,<sup>2</sup> and JAMES E. LINGEMAN, M.D.<sup>1</sup>

### ABSTRACT

**Topiramate is a recently developed antiepileptic medication that is becoming more widely prescribed because of its efficacy in treating refractory seizures. Urologists should be aware that this medication can cause metabolic acidosis in patients secondary to inhibition of carbonic anhydrase. In addition, a distal tubular acidification defect may result, thus impairing the normal compensatory drop in urine pH. These factors can lead to the development of calcium phosphate nephrolithiasis. We report the first two cases of topiramate-induced nephrolithiasis in the urologic literature.**

### INTRODUCTION

**T**OPIRAMATE IS A RECENTLY INTRODUCED anti-epileptic medication that is used adjunctively in the treatment of partial or refractory seizures. Trials have demonstrated that topiramate does provide a significant benefit in these cases, with greater than 40% of patients having a 50% or greater reduction in seizure frequency.<sup>1</sup> In addition, there are reports of efficacy for other disorders such as bipolar disorder and trigeminal neuralgia.

The side effect profile of topiramate is generally favorable. However, it is a known inhibitor of the enzyme carbonic anhydrase, and chronic use can lead to the development of metabolic acidosis. As a result, patients may be at risk to form stones over time. Herein, we report two cases of nephrolithiasis that were likely induced by topiramate use. After analyzing the metabolic work-up results of these patients, we see evidence that topiramate may also cause a distal tubular acidification defect, thus influencing the type of stone formed. According to a literature review, this is the first report of this phenomenon in the urologic literature.

### CASE REPORTS

#### *Case 1*

A 21-year-old woman had a medical history significant for primary generalized epilepsy. The patient developed her first stone at age 16, a 4-mm obstructing calculus in the distal right

ureter. Serum chemistry studies at the time of this episode were normal (chloride 103 mEq/L, bicarbonate 25 mEq/L). Ureterscopy and basket extraction of the stone was performed. Analysis at this time revealed the stone to be 87% calcium oxalate dihydrate and 13% calcium oxalate monohydrate. The patient had a family history of nephrolithiasis (grandparents, aunt).

The patient was started on topiramate (200 mg po bid) for seizure control after her first stone episode. She did well from a urologic standpoint until she presented with left renal colic. This time, the patient's chemistry assays revealed a decreased serum bicarbonate level of 20.8 mEq/L and elevated chloride of 112 mEq/L. An intravenous urogram (IVU) demonstrated a 2-mm left distal ureteral filling defect presumed to be a calculus. Conservative therapy was instituted, but the patient continued to be symptomatic. She was taken to the operating room, where cystoscopy and a retrograde pyelogram were performed. No filling defect was demonstrated, and a ureteral stent was placed. The stent was subsequently removed, and follow-up IVU showed no evidence of calculi. The patient was thought to have passed her stone.

A metabolic work-up was initiated. The 24-hour urine results showed a low citrate excretion of 332 mg/day (normal >450 mg/day), with elevated daily excretion of calcium, oxalate, and sodium at 435 mg [normal <200 mg for females], 64 mg (normal 20–40 mg), and 377 mEq (normal 50–150 mEq), respectively. The urine pH was 6.7. The low serum bicarbonate value and hypocitraturia were consistent with systemic acidosis. The patient was begun on a regimen of potassium citrate, 10 mEq bid.

Recently, the patient required ureteroscopic extraction of an-

<sup>1</sup>Clarian Health Partners, Methodist Hospital of Indiana and Indiana University School of Medicine, Indianapolis, Indiana.

<sup>2</sup>The Division of Urology, Department of Surgery, Albany Medical College, Albany, New York.

other 3.5-mm right distal ureteral stone after again presenting with colic. Serum chemistry assays demonstrated a continued low bicarbonate concentration of 19 mEq/L, with an elevated chloride concentration of 111 mEq/L. Stone analysis this time demonstrated the calculus to be 100% calcium phosphate. The patient has since been weaned off topiramate and has begun another antiepileptic medication regimen.

### Case 2

A 59-year-old man presented with acute left flank pain and associated nausea and vomiting. Laboratory work-up included two urinalyses showing a pH of 6.5, with red blood cell counts ranging from 4 to 6 per high-power field (HPF) and white blood cells from 0 to 1 per HPF. A urine culture was negative. Serum chemistry findings were normal. Serum calcium was 9.6 mg/dL (normal 8.4–10.8 mg/dL), and the parathyroid hormone concentration was 34 pg/mL (normal 11–54 pg/mL). An IVU revealed mild left hydronephrosis with a 7-mm distal left ureteral calculus less than 1 cm above the ureterovesical junction. The patient had no history of calculus disease or gout and no family history of stones. He was admitted for intravenous hydration and pain control and spontaneously passed the stone the following morning.

The patient's medical history was significant for a back injury resulting in chronic left upper extremity pain. Because of the chronic pain, muscle spasms, and numbness affecting this extremity, the patient had been followed by a pain service and the neurology department. He had been on various pain regimens, including COX-2 inhibitors, tricyclic antidepressants, and narcotic analgesics (hydrocodone) for more than 3 years. Most recently, the patient was placed on muscle relaxants that had to be discontinued secondary to intolerable side effects. His neurologist then started him on a trial of topiramate for control of his debilitating symptoms. The patient had been taking topiramate for 3 months with virtually complete relief of symptoms when he presented with left renal colic.

After resolution of the stone episode, the patient underwent a full metabolic work-up. No serum chemistry values prior to initiation of topiramate were available. The stone was 92% calcium hydrogen phosphate (brushite), 5% calcium phosphate (hydroxyapatite), and 3% calcium oxalate monohydrate. The 24-hour urine tests revealed the following daily excretion values: calcium 283 mg (normal <250 mg for males), citrate 49 mg (normal >450 mg), uric acid 842 mg (normal <800 mg), sodium 234 mEq (normal 50–150 mEq), and phosphorus 1.95 g (normal 0.6–1.2 g). The urine pH was 6.7.

Despite warnings about the potential development of further stones, the patient refused to discontinue his topiramate regimen. He agreed to a trial of potassium citrate but has not returned for follow-up. Unfortunately, his compliance with potassium citrate is unknown at present.

## DISCUSSION

Topiramate is an antiepileptic medication classified as a sulfamate-substituted monosaccharide. Because of its proven efficacy in treating partial and refractory seizures, use of this drug has become increasingly prevalent. Wider usage of this

medication can also be attributed to its side effect profile, which is generally better than that of older antiepileptic medications. The most common sequelae appear to be related to central nervous system effects: dizziness, fatigue, paresthesias, ataxia, somnolence, and abnormal thinking.<sup>2</sup> The onset of side effects appears to be related to the dose titration curve, with rapid increases in dosage predisposing to adverse events.<sup>1</sup>

Topiramate also inhibits the enzyme carbonic anhydrase at the proximal renal tubule, although its anticonvulsant effect is likely independent of this mechanism.<sup>2</sup> Reduction in carbonic anhydrase activity impairs the exchange of  $H^+$  for  $Na^+$  in the proximal tubule, as well as the reabsorption of  $HCO_3^-$ . The inhibitory properties of topiramate are quite weak compared with those of true carbonic anhydrase inhibitors such as acetazolamide.<sup>3</sup> As clinical experience with topiramate has accumulated, however, it is becoming increasingly clear that significant metabolic acidosis can develop in patients over time.<sup>2,4</sup> A recent study in a pediatric epilepsy population revealed that although the degree of acidosis was not enough to cause overt symptoms, a decrease in serum bicarbonate levels of >10% was still present in the majority of the patients.<sup>5</sup>

In the initial trials of topiramate, a 1.5% incidence of nephrolithiasis was noted in 1200 patients.<sup>4</sup> Past groups have attributed the etiology of these stones to the hypocitraturia resulting from carbonic anhydrase inhibition.<sup>6</sup> It is well known that the urinary citrate concentration decreases dramatically when systemic acidosis is present, thus lowering the solubility of urine calcium and increasing the risk of calcium nephrolithiasis.

Notably, our two patients formed calcium phosphate stones after initiating topiramate therapy. The majority of other stones obtained from topiramate patients have been comprised of calcium phosphate as well.<sup>7</sup> In both of our cases, the patients' 24-hour urine pH was 6.7, bringing into question the premise of carbonic anhydrase inhibition as the primary factor in stone formation. The bicarbonate loss that occurs after inactivation of carbonic anhydrase creates a physiologic situation analogous to a proximal renal tubular acidosis (type 2 RTA). It is well known that patients with type 2 RTA do not form stones, as renal acidification mechanisms remain intact. The fact that our acidotic patients had a urine pH of 6.7 after ample time had elapsed to allow a compensatory pH decrease suggests that a distal acidification defect (i.e., type 1 RTA) is also being caused by the chronic use of topiramate. This idea is supported by previous work showing that carbonic anhydrase inhibitors may interfere with  $H^+$  secretion by the distal tubule.<sup>8</sup>

In view of these findings, we believe that topiramate induces stones through two separate mechanisms. First, metabolic acidosis is initiated through inhibition of carbonic anhydrase at the proximal tubule. Hypocitraturia results, which elevates the risk of calcium stone formation. Second, the drug may affect the acidification mechanisms of the distal tubule, causing the urine to be relatively alkaline despite the systemic acidosis. This would explain the preponderance of calcium phosphate stones in similar cases. In the future, results of ammonium chloride loading tests may clarify whether a distal acidification defect exists, as the urine pH should theoretically not decrease below 5.5 in these patients.

Of our two patients, the first presented a more complex situation, as she had onset of nephrolithiasis early in her life. This

event signifies the existence of risk factors for stones even prior to the institution of topiramate. However, it is important to note that her initial stone was comprised mainly of calcium oxalate dihydrate, whereas her most recent episode of nephrolithiasis involved a pure calcium phosphate stone. A review of the patient's serum and urine tests support the view that her latest stone problems likely resulted from chronic use of topiramate, by the mechanisms outlined previously.

Because topiramate use is becoming more prevalent, urologists should be aware of the potential risk of nephrolithiasis in these patients. Serum chemistry studies should be checked regularly to detect the onset of metabolic acidosis. In addition, patients on long-term topiramate therapy should undergo periodic bone densitometry testing to detect early calcium loss secondary to acid buffering by bone. It is prudent to initiate general preventative measures against stone formation in these patients, such as high fluid intake, limited sodium intake, and consumption of citrate-containing fluids such as lemonade. Consideration should also be given to prophylactic potassium citrate supplementation to minimize the development of calculi, as these patients are likely to be hypocitraturic.

### CONCLUSION

Topiramate is an effective medication used primarily in the treatment of partial or refractory seizure disorders. Long-term use of this drug can produce a significant metabolic acidosis in certain individuals through an inhibitory effect on carbonic anhydrase. In addition, chronic topiramate use may result in a distal tubular acidification defect, which in turn leads to a higher risk of developing calcium phosphate nephrolithiasis. Urologists should inform patients taking topiramate of the potential

risk of nephrolithiasis and make appropriate recommendations to minimize the risk of stone formation. Further investigation is needed to completely elucidate the mechanism of stone formation from chronic topiramate therapy.

### REFERENCES

1. Walker MC, Sander JW. Topiramate: A new antiepileptic drug for refractory epilepsy. *Seizure* 1996;5:199.
2. Stowe CD, Bollinger T, James LP, et al. Acute mental status changes and hyperchloremic metabolic acidosis with long-term topiramate therapy. *Pharmacotherapy* 2000;20:105.
3. Dodgson SJ, Shank RP, Maryanoff BE. Topiramate as an inhibitor of carbonic anhydrase isoenzymes. *Epilepsia* 2000;41(suppl 1):S35.
4. Wilner A, Raymond K, Pollard R. Topiramate and metabolic acidosis. *Epilepsia* 1999;40:792.
5. Takeoka M, Holmes GL, Thiele E, et al. Topiramate and metabolic acidosis in pediatric epilepsy. *Epilepsia* 2001;42:387.
6. Wasserstein AG, Rak I, Reife RA. Investigation of the mechanistic basis for topiramate-associated nephrolithiasis: Examination of urinary and serum constituents. *Epilepsia* 1995;36(suppl 3):S153.
7. Wasserstein AG, Rak I, Reife RA. Nephrolithiasis during treatment with topiramate. *Epilepsia* 1995;36(suppl 3):S153.
8. Weiner IM. Diuretics and other agents employed in the mobilization of edema fluid. In: Gilman AG, Rall TW, Nies TW, et al (eds): *Goodman and Gilman's The Pharmacologic Basis of Therapeutics*, ed 8. New York: Pergamon Press, 1990, pp 713-731.

Address reprint requests to  
*Ramsay L. Kuo, M.D.*  
1801 North Senate Blvd, Suite 220  
Indianapolis, IN 46202

*E-mail:* rkuo@iupui.edu