Headache
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ISSN 0017-8748
doi: 10.1111/head.12480
Published by Wiley Periodicals, Inc.

Expert Opinion

The Risk and Management of Kidney Stones From the Use of Topiramate and Zonisamide in Migraine and Idiopathic Intracranial Hypertension

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Key words: kidney stone, topiramate, zonisamide, migraine, idiopathic intracranial hypertension

(*Headache* 2015;55:161-166)

Kidney stone formation may complicate the treatment of patients with migraine and idiopathic intracranial hypertension (IIH) with topiramate (TPM) and zonisamide (ZNS).

CASE HISTORY

A 40-year-old woman has a 15-year history of migraine without aura that has been chronic for 5 years. While on TPM 100 mg daily for 2 years without side effects, her migraine frequency has decreased from 20 days per month to 6 days per month. She then developed a first-time kidney stone that passed spontaneously. Upon analysis, the stone was determined to be calcium phosphate.

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Accepted for publication November 14, 2014.

QUESTIONS

What is the type of kidney stones that form and their pathophysiology? What is the frequency of kidney stones in migraineurs on TPM and ZNS and the general population? Is the risk dose and time dependent? Is a prior history of kidney stones a contraindication to use of either medication? Is formation of kidney stones a contraindication to ongoing use of TPM or ZNS? If migraineurs who develop a kidney stone(s) on TPM continue the drug, is there any way to prevent further stone formation? In patients with IIH, is the risk of kidney stone formation a contraindication to combined use of TPM and acetazolamide (ATZ)?

EXPERT COMMENTARY

TPM was first synthesized in 1979. It is rapidly absorbed systemically and has a linear steady-state pharmacokinetic profile that peaks in 2 hours and has a half-life of 21 hours.[1] It is not a significant hepatic enzyme inducer and is renally cleared. TPM has been approved by the US Food and Drug Administration for the treatment of epilepsy since 1996 and for

Conflict of Interest: None.

Financial Support: BMG acknowledges the generous support of the Heffer Family Foundation, who underwrote the preparation of this manuscript.

migraine prophylaxis since 2004. TPM exerts its drug effects through various mechanisms, including blockade of voltage-gated sodium and calcium channels, inhibition of glutamate receptor function, potentiation of γ-aminobutyric acid activity, and inhibition of carbonic anhydrase II and IV.[2] Trials have shown that TPM reduces mean number of migraine days in both episodic and chronic migraine sufferers and is associated with a >50% reduction in headache days.[3-5] The mean dose of TPM used in these studies was 100 mg/day, although doses of 200 mg/day and higher were used in other migraine and epilepsy studies. As TPM is widely used in the treatment of epilepsy, migraine, mood disorders, and weight loss, it is prudent to be aware of the potential adverse effects of the drug. In migraine studies, adverse effects occur in 65-82% of subjects on TPM. Common adverse effects include paresthesias, fatigue, weight loss, cognitive complaints, dry mouth, taste perversion, and nausea.[3,5] Less common adverse effects of TPM include renal stones, acute angle closure glaucoma, palinopsia, Stevens–Johnson syndrome, tremor, and myoclonus.[1] Although renal stones, attributed to the carbonic anhydrase inhibitor activity of TPM, are a less common adverse effect, it behooves clinicians to be aware of its occurrence as TPM is one of the more frequently used agents for migraine prophylaxis. Other medications with carbonic anhydrase inhibitor activity used in the management of headache disorders include ZNS and ATZ. ZNS has been used as an off-label preventive treatment for migraine while ATZ is considered to be the first-line drug of choice in IIH.

Type and Pathophysiology of Stone Formation.— Kidney stones form when the balance between crystallizing solute, inhibitors of stone formation, and crystal interaction with the renal epithelium favor stone formation.[6] The majority of kidney stones reported with TPM and ZNS are calcium phosphate or calcium oxalate.[7-10] The etiology of kidney stone formation with these medications is believed to be due to inhibition of carbonic anhydrase type II and IV in the proximal and distal renal tubules, leading to a mixed renal tubular acidosis (RTA). The data to support this mechanism come from a detailed analysis of a patient with a rare congenital deficiency of type II carbonic anhydrase revealing both proximal and distal defects in urinary acidification and consistent urine and blood findings in patients taking carbonic anhydrase inhibitors.[9,11] Welch et al described the metabolic derangements that occur in patients taking TPM in both a cross-sectional study of 32 patients and a short-term longitudinal study of 7 patients vs healthy volunteers.[12] Factors leading to the elevated risk of nephrolithiasis were those expected with a carbonic anhydrase inhibitor: hyperchloremic metabolic acidosis with hypercalciuria, hypocitraturia, increased fractional excretion of bicarbonate, elevated urine pH, and increased urinary saturation of calcium phosphate. Citrate is an inhibitor of stone formation as it forms a soluble complex with calcium; hypocitraturia is a consistent finding among all published reports of TPM-associated risk for nephrolithiasis.[7] Hypercalciuria favors the formation of calcium stones and elevated urine pH reduces the solubility of calcium phosphate, thereby favoring crystal formation. Patients with congenital deficiency of type II carbonic anhydrase suffer from osteopetrosis, cerebral calcifications, and growth retardation.[11] It is not known why patients who take carbonic anyhdrase inhibitors more prominently manifest the classic distal RTA propensity to form renal stones.[12,13]

Frequency of Kidney Stones on TPM and ZNS.— Most studies on TPM and renal stones are derived from epileptic patients, as TPM has been used for a longer period of time for epilepsy. One of the largest studies to date looked at the long-term safety of epileptic patients taking TPM for 5.3 years with doses ranging from 200 to 600 mg. The incidence of nephrolithiasis not requiring surgery in these patients was 1.5%.[14] Other studies report prevalence of symptomatic nephrolithiasis to be 2.1-10.7%, while asymptomatic nephrolithiasis occurred in 20% of TPM users.[7,15] Nephrolithiasis has also been reported in children, with an incidence of asymptomatic stones in 5.2% increasing to 54% in non-ambulatory children.[8,16] Meanwhile, ZNS, another antiepileptic agent that has been shown to be as effective as TPM and better tolerated, has a reported incidence of symptomatic renal calculi in 1.2% of patients while incidence of asymptomatic renal calculi occurred in 2.6% of

patients.[17,18] Post-marketing surveillance over 3 years in the United States reported renal calculi in 0.02% of patient exposure-years to ZNS.[19] In contrast, ATZ has a much higher incidence of renal calculi ranging from 15% to 36%.[20,21] Compared with ATZ, TPM and ZNS have 100-200 times less carbonic anhydrase inhibition, and this explains the higher prevalence of renal calculi in patients taking ATZ.[22,23]

In the general adult US population, overall lifetime prevalence of kidney stones is 5.2%.[24] The risk of renal stone formation is 2-4 times higher in TPM users when compared with the general population.[25]

Is the Risk of Renal Stones Dose and Duration Dependent?—While other adverse effects such as paresthesias, cognitive complaints, and weight loss appear to be dose dependent in clinical trials,[3] it is still unclear if renal stone formation is dose and duration dependent. Studies that looked at the association between dose and duration have been mixed.[19] There was no apparent relationship between stone formation and duration of TPM therapy in Shorvon's review, although there was a suggestion of a relationship to dose.[14] A retrospective study found that TPM dose and duration inversely correlated with the urinary citrate level, which increases the risk of stone formation.[9] In clinical trials, the degree to which serum bicarbonate levels were lowered occurred in a dose-dependent manner with the incidence of renal calculi, varying from 1% at TPM 100 mg/day and 2% at TPM 200 mg/day compared with 0% for TPM 50 mg/day and placebo.[1] Dell'Orto's review of the topic did not find a relationship between the degree of acidosis and TPM dose or level, suggesting that genetic factors may contribute to the risk of developing acidosis.[7]

Is a Prior History of Kidney Stones a Contraindication to Use of Either TPM or ZNS?—Prior history of a stone is not an absolute contraindication for use of TPM/ZNS. The composition of the stone and metabolic work up may provide clues as to the underlying cause, be it a structural, infective, or metabolic process. A standard stone work-up to identify the underlying etiology is indicated.[26,27] In the absence of a continued predisposing risk factor, it is reasonable to consider the use of TPM or ZNS. However, in patients with an already increased risk of stone formation from an underlying cause, care should be taken and an alternate agent may be considered. There is no proven method for predicting or preventing the effect of TPM on acid–base balance in patients.[13]

Is Stone Formation a Contraindication for Ongoing Use?—Although a risk factor for calcium containing stones, it is reasonable to continue treatment after discussion if the benefits of treatment outweigh the risks of recurrent stones. Prior case reports that continued the use of ZNS in epileptic patients with doses ranging from 400 to 600 mg/day and follow up to 45 months did not result in recurrence of calculi.[28]

Is There Any Way to Prevent Further Stone Formation?—There are no published trials of treatment interventions to reduce the risk of TPM or ZNS associated renal stones. General stone prevention recommendations including hydration to maintain a daily urine output of 2.5 L to minimize supersaturation of urine solute and a low-sodium diet to help reduce hypercalciuria can be safely recommended for patients.[6,27] In addition, insights can be gained from available reports of treatment interventions for patients with risk factors for stones due to diseases with similar distal RTA pathophysiology. Oral potassium citrate is a mainstay in treatment of renal stones with utility in correcting metabolic acidosis, hypocitraturia and hypercalciuria.[6] Potassium citrate is available in both tablet and liquid formulations.

Domrongkitchaiporn et al reported on the effect of potassium citrate supplementation on the correction of urinary abnormalities in a population of children with idiopathic distal RTA.[29] In this prospective study of 8 children, they found that a dose of 4 mEq/kg/day resulted in normalization of the urine calcium-to-creatinine ratio, phosphate-to-citrate ratio, calcium-to-citrate ratio, citrate-to-creatinine ratio, and urinary saturation of calcium oxalate. However, the elevation in urinary saturation of calcium phosphate was not normalized. This study did not report on incidence of renal stones.

Preminger et al provided potassium citrate therapy to 9 incomplete distal RTA patients suffering from recurrent nephrolithiasis with mean follow up of 34 months. Urine studies on citrate found normalization of urine citrate and calcium, improvement in the relative saturation ratio for calcium oxalate, but no

change in the saturation ratio for calcium phosphate. Prior to therapy the patients passed an average of 13.1 stones per year. In the 3 years of follow up on citrate therapy, none of the patients formed a new stone.[30] Fabris et al reported retrospective data on 97 patients with medullary sponge kidney (MSK) (an anatomic disorder of the kidney associated with incomplete distal RTA and recurrent calcium oxalate and calcium phosphate stones) who received treatment with potassium citrate. Among patients with MSK and an additional stone risk factor, treatment with potassium citrate reduced the stone event rate from 0.58 to 0.10 stones/year per patient ($P < .001$).[31]

Finally, use of citrate for epileptic children treated with a ketogenic diet may provide additional support for use of citrate in patients on TPM or ZNS. The ketogenic diet is well known to increase the risk of renal stones due to the induction of metabolic acidosis, hypercalciuria, and hypocitraturia. In addition, many of these patients are also on a carbonic anhydrase inhibitor. McNally et al published a retrospective study of 313 children treated in sequential time periods. Of 195 patients treated from 2000 to 2005, 42% were on a carbonic anhydrase inhibitor in addition to the diet. Only patients with hypercalciuria were also treated with citrate. Seven percent of the patients had a renal stone event. In the years from 2006 to 2008, 106 children were treated with the diet and citrate regardless of urinary calcium levels. Fifty percent were also on a carbonic anhydrase inhibitor. In this group, only 0.9% had a stone event ($P = .02$).[32]

In all of these studies, urine pH rose on citrate therapy. This raises the concern that citrate therapy could increase the risk of calcium phosphate crystallization in the distal tubule. However, in these studies, citrate therapy reduced the rate of stone events despite higher urine pH.

A few authors have reported outcomes of individual patients treated with citrate and TPM or ZNS. Two patients managed in a stone clinic were maintained on TPM with the addition of potassium citrate after a stone event. Evaluation of urinary parameters on citrate revealed complete correction of hypocitraturia without an increase in calcium phosphate supersaturation.[9] A patient following a stone on ZNS was continued on the drug with the addition of calcitrate and had no stone recurrences up to 45 months of follow up.[28] The same group also treated a patient on ZNS after a stone with increased fluid intake and drug continuation. The patient had no recurrence up to 42 months of follow up.[28] In contrast, a patient reported by Lamb et al treated with increased fluid intake and potassium citrate after a stone event on high-dose TPM (1000 mg/day) had a stone recurrence at 2 years of follow up.[33] It should be noted that this patient elected to continue TPM because of the quality of life seizure control provided by the medication. Other studies have also reported patient preference to continue these medications despite renal stone events due to overall quality of life considerations.[34]

As the data to guide management of patients with nephrolithiasis on TPM or ZNS are limited, decisions on therapy must be individualized with shared decision making for each patient. A patient who forms a stone while on TPM or ZNS therapy should undergo a standard metabolic stone workup to establish the baseline urinary and serum parameters.[27]

If the decision is made to continue the medication and institute medical therapy with the goal of reducing the risk of recurrent nephrolithiasis, potassium citrate is the agent of choice. A total daily dose of 20-80 mEq of potassium citrate in 3 or 4 divided doses could be considered as a starting dose.[9,30,31] Standard follow up as recommended by the American Urological Association is indicated to allow assessment of response and adjustment of therapy.[27] Follow up should include repeat 24-hour urine and serum analysis at 6 months and then yearly along with yearly imaging. Some experts recommend re-evaluation 6-8 weeks after initiation of therapy or monthly during titration of the citrate dose.[31,35] Urine pH should be included in the monitoring plan as higher urine pH promotes calcium phosphate crystallization. The goal of therapy is normalization of urine citrate and calcium concentrations while maintaining the urine pH below 7.5.[31] Of note, Welch et al reported that patients on TPM had lower creatinine clearances.[12] This finding has not been reported by

other investigators, but given the paucity of data it may be prudent to include monitoring of renal function for patients on these medications.

In IIH, Is the Risk of Stone Formation a Contraindication for ATZ and TPM Combination?—ATZ improves visual outcome in IIH, with risk of renal stones reported as 2.3%.[36] In patients who have had renal stones before, reported recurrence with ATZ is as high as 50%.[28] There is no study looking at the risk of stone formation with combination use of TPM and ATZ.

In a review of 59 patients in the clinical trial population treated for epilepsy who used the combination of ZNS and TPM, none of them developed stones. Further post-marketing surveillance of those on combination TPM and ZNS resulted in only 1 out of 25 patients developing stones.[19] As TPM and ZNS both have less than 100-200 times the carbonic anhydrase inhibitor activity compared with ATZ, it may be assumed that the risk of stone with combined ATZ and TPM would only confer a slight increase in the risk of stone formation as compared to the risk in ATZ alone.

CONCLUSION

In summary, patients treated with TPM, ZNS, or ATZ are at increased risk for metabolic derangements predisposing to renal stone formation due to the carbonic anhydrase inhibition of these medications. There is no reliable method to predict which patients will develop this side effect. The data are mixed on the relationships of dose and duration to risk for renal stone formation. General stone prevention measures of hydration and low sodium intake can be recommended for all patients on TPM or ZNS. For those who develop metabolic acidosis or experience a stone and the benefits of continuing the medication outweigh the risks, potassium citrate therapy may be considered with the caveat that there is a potential increased risk of calcium phosphate stone formation, and no clinical trial data exist to guide treatment for this particular group of patients. Comanagement with a nephrologist or urologist is recommended. Prospective trials of potassium citrate therapy for patients on TPM and ZNS are indicated. As with any treatment-related decision, an open discussion with the patient with regard to risks and benefits of treatment is paramount.

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