Refractory Uric Acid Nephrolithiasis Dissolution using Phentermine/Topiramate: A Case Report

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KEYWORDS

Nephrolithiasis, Uric Acid, Obesity, Alkalinization, Phentermine, Topiramate

ABSTRACT

Uric acid is one of the few kidney stone minerals that can be dissolved using oral alkalinization therapies such as sodium bicarbonate or potassium citrate. We report a case of a morbidly obese female whose recalcitrant uric acid stone burden was eliminated using the weight-loss medication phentermine/topiramate (Qsymia), a combination metabolic stimulant and carbonic anhydrase inhibitor. Pre- and post-dissolution 24-hour urine studies and computed tomography (CT) images are included along with a proposed mechanism of action of this medication. To our knowledge, this is the first description of a non-alkaline oral therapy such as Qsymia, used alone, for uric acid stone dissolution. Additional investigation of this medication in the setting of refractory uric acid nephrolithiasis is warranted.

INTRODUCTION

Metabolic syndrome is associated with various risk factors that contribute to kidney stone development, such as excessive ingestion and excretion of dietary acids and a compromised urinary buffering system by impaired renal ammoniagenesis[1]. The resultant increased urinary acid excretion and lowered urine pH drive uric acid supersaturation and increase the risk of uric acid stone formation in these individuals[2]. Stones containing uric acid account for approximately 10% of all kidney stones, with a greater uric acid stone risk noted in patients with body mass index (BMI) greater than 30. Some studies also indicate a strong association between obesity and nephrolithiasis in women and men[3,4]. For patients afflicted with uric acid stones, the American Urological Association Medical Management of Kidney Stone Guidelines and the American Family Physician guidelines recommend potassium citrate as an oral alkalinizing agent to help prevent and possible dissolve uric acid stones by raising urine pH[5]. Additionally, lifestyle approaches have shown associated reductions in stone burden and risk such as Dietary Approaches to Stop Hypertension (DASH), fluid, vegetable, and fruit intake[6]. However, literature related to weight loss medications and reducing stone formation is limited, and no standard of care or graded recommendation exists regarding the use of weight loss medication for the treatment of uric acid nephrolithiasis. Herein, we report a novel approach toward the pharmacological treatment of refractory uric acid nephrolithiasis through using Qsymia, a weight-loss medication with the side effect of urinary alkalinization.

CASE PRESENTATION

A 57-year-old super morbidly obese (320#, BMI=53) female with type 2 diabetes mellitus presented to nephrology in 2012 for recurrent passages of small uric acid stones. In light of normal serum uric acid level, her stone disease was managed using oral alkalinization medications. In 2013, she switched from potassium citrate (20 meq BID) to low dose sodium bicarbonate (1300 mg BID) due to diarrhea, nausea, vomiting, and general citrate intolerance. The patient continued to pass stones monthly and was unable to tolerate increases in sodium bicarbonate dosing. Two separate 24-hour urine samples were collected during this time period (Table 1 - May 2012, December 2016), both demonstrating low urine volume (1.4-1.5 L), low urine pH (5.25-5.33), and elevated uric acid supersaturations (2.17 – 3.45). In 2017, she was referred to urology for surgical management of an obstructing 12 mm left ureteral stone. Over the subsequent four years, she had 16 different abdominal and pelvic computed tomography (CT) scans (primarily in the ED setting during stone passage) and five separate ureteroscopies, three of which were bilateral in nature.

Table 1: Recurrent uric acid stone former 24 hr urine values, variables labeled with normal range per day.

Date	Volume (>2 liters)	SS CaOx (<2)	Calcium (<200mg)	Oxalate (< 40 mg)	Citrate (>550 mg)	SS CaP (< 2)	pH (5.8 – 6.2)	SS UA (<2)	Uric Acid <0.75 gm)
5/8/23	1.25	11.00	245	36	413	0.48	5.289	4.40	0.946
12/15/22‡	1.22	12.19	166	48	978	1.82	6.144	1.55	1.267
11/10/22†	1.98	8.41	362	39	531	1.64	5.934	1.71	1.517
10/7/21*	2.66	3.41	188	34	630	0.78	6.446	0.32	1.057
5/18/21	1.51	8.30	178	41	972	0.37	5.326	3.08	0.830
3/25/20	1.46	6.64	111	39	734	0.21	5.325	2.70	0.437
12/5/16	1.50	5.71	138	33	889	0.28	5.253	3.45	0.357
5/25/12	1.60	6.59	178	30	855	0.44	5.483	2.17	0.744

Date	Sodium (<150 mmol)	Potassium (<100 mmol)	Magnesium (<120 mg)	Phosphorus (<1.2 mg)	Ammonium (<60 mmol)	Chloride (<250 mmol)	Sulfate (<80 meq)	Urea Nitrogen (6-14 gm)	Catabolic Rate (0.8–1.4 gm/kg)
5/8/23	161	62	84	0.934	70	198	49	12.89	0.8
12/15/22‡	181	51	41	1.043	45	143	32	9.56	0.6
11/10/22†	284	55	65	1.423	64	266	51	14.4	0.9
10/7/21*	369	52	42	0.859	40	347	35	11.13	0.7
5/18/21	187	56	55	1.280	67	185	42	12.05	1.3
3/25/20	158	66	27	1.037	33	153	43	11.03	0.7
12/5/16	183	72	28	1.518	28	170	46	13.32	0.8
5/25/12	177	56	50	1.049	23	144	26	10.67	0.7

* - 24 hour urine performed while patient on phentermine/topiramate 7.5 mg/46 mg

†- 24 hour urine performed while patient on topiramate 25 mg alone

‡- 24 hour urine performed while patient on topiramate 50 mg alone

On January 25, 2021, the patient had a CT scan performed (Figure A/B insets) showing five new bilateral kidney stones (3 right, 2 left) roughly 4 months after bilateral ureteroscopic stone removal. Having failed medical management, we explored the option of weight loss and urinary alkalinization with pharmaceutical Qsymia®, a combination of phentermine, a sympathomimetic amine anorectic that increases metabolism, and topiramate, an anti-epileptic carbonic anhydrase inhibitor that reduces cravings. The patient collected a 24-hour urine specimen on 5/18/21 (Table 1) and began taking low dose Qsymia 3.75 mg/23 mg on 5/20/21. Fourteen days later, her dose escalated to 7.5 mg/46 mg. On July 12, 2021, seven weeks after beginning her medication, the patient had a follow-up CT scan, demonstrating complete dissolution of all five kidney stones (Figure inset C/D). A follow-up 24-hour urine on 10/7/21 showed an increase in urine volume to 2.66 liters and in urine pH to 6.45 with a drop in uric acid supersaturation to 0.32. Over the next six months, the patient's weight dropped to 283 pounds (total 37-pound weight loss), and she had no ED visits or reports of stone passage. She remained on this medication until the fall of 2022, when she complained of lack of continued weight loss as well as loss of insurance. Due to financial reasons, she stopped Qsymia and was placed on generic topiramate 25 mg (alone) with repeat 24-hour urine testing done on 11/10/22 showing a decrease in her urine pH to 5.934. As a result, her topiramate dose was escalated to 50 mg, and repeat testing on 12/15/22 showed a maintained urine pH of 6.144. Five months later, the patient self-discontinued the topiramate citing "brain fog," and a follow-up 24-hour urine 5/8/23 showed her urine volume, pH, and uric acid SS had all regressed back to her pre-medication levels. At her most recent urology clinic visit in October 2023, she was noted to have weight regain to 310 pounds. Although she reported recurrence in her monthly passage of small kidney stones, her abdominal CT showed no stones or hydronephrosis in either kidney and, notably, she has not required surgical intervention for stone disease since 2020.

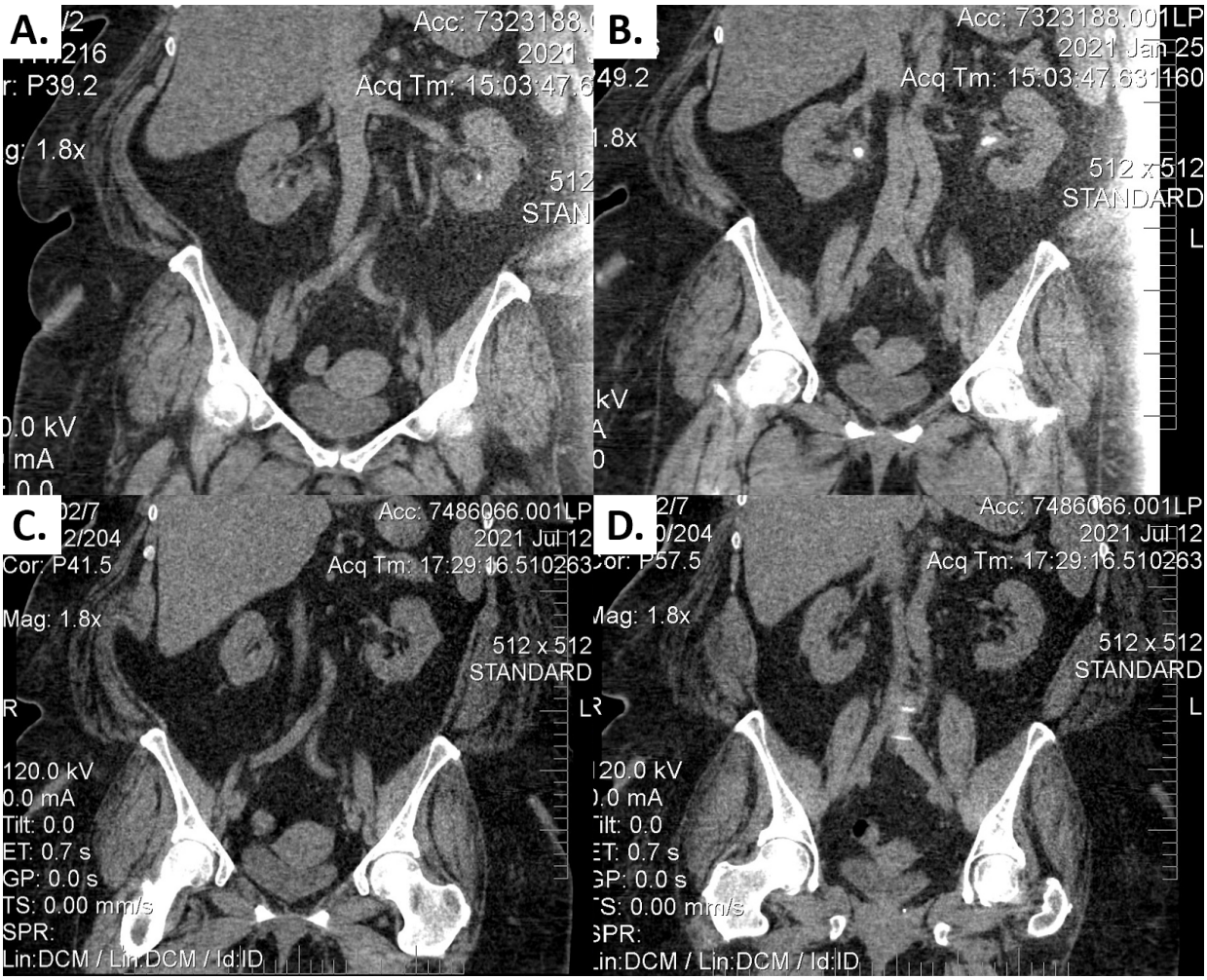

Figure 1. Abdominal computed tomography (CT) of a patient with bilateral uric acid kidney stones before (A,B) and after (C,D) administration of Qsymia® 7.5 mg/46 mg. (A,B) Coronal CT sections demonstrating lower pole and renal pelvis calculi (red arrows). (C,D) Coronal CT demonstrating complete stone dissolution after 3 months on phentermine 7.5 mg/topiramate 46 mg (Qsymia®).

DISCUSSION/CONCLUSIONS and RECOMMENDATIONS

The cornerstone of medical management for uric acid stones urinary alkalinization, commonly through administration of either oral potassium citrate or sodium bicarbonate.[7] The aim of alkalinization is to achieve a urinary pH ranging from 6.5 – 7, which renders uric acid completely soluble in urine. Other pharmacologic agents, such as xanthine oxidase inhibitors febuxostat or allopurinol, may be used as an adjunct with alkalinizing agents to reduce urinary acid excretion. Although these adjuncts effectively lower serum and urinary uric acid levels, they have been shown to have minimal effect on an individual's stone burden or on long-term uric acid stone outcomes. [8,9] The challenges related to the use of potassium citrate for urinary alkalinization are highlighted in this case report. Patients are often non-compliant with alkaline medications due to the number of pills (sometimes up to 12/day) and gastrointestinal side effects, namely abdominal pain, nausea, or diarrhea[10] - symptoms experienced by our patient.

Given our patient's citrate intolerability and degree of symptomatic recurrences requiring surgical intervention, we started Qsymia® (combination phentermine/topiramate), an FDA-approved medication for weight loss in patients with morbid obesity.[11] One of its components, topiramate, falls under the class of drugs known for its inhibitory effect on carbonic anhydrase activity in the proximal convoluted tubule of the kidney, reducing bicarbonate reabsorption and raising urine pH [12-15]. In fact, the package insert lists excessive urine pH and formation of alkaline-based calcium phosphate stones as a potential side effect of this medication – a finding that has been noted by a number of authors[12-15]. Based on our patient's lab values and imaging, Qysmia was effective for weight loss and urinary alkalinization. Not only did her existing uric acid stones (Figure 1) completely dissolve within 4 months by moderate dose (7.5 mg/46 mg) therapy, but their formation was completely inhibited while the patient was compliant on medication. Interestingly, she continued topiramate alone after discontinuing Qsymia, and this by itself also seemed to effectively raise her urine pH. Her 24-hr supersaturation (SS) of uric acid, a calculated value based off measured urinary values and a driver of urinary crystallization, was lowest while on topiramate therapy, highlighting the importance of a high urine pH to medically treat uric acid stones. The patient reached her weight loss plateau roughly 6 months after starting her medications, a commonly reported phenomenon after prescribing weight loss medication. The development of "brain fog" cognitive deficits (language, attention, and memory) that led to medication cessation is also a commonly reported side effect that has been shown to improve once the medication is stopped. Finally, the kidney responds to excessive urinary alkalinization and metabolic acidosis by reducing the excretion of urinary citrate. In our patient, a small decline in urine citrate is seen in 2021 and 2022 labs but was most pronounced when she was completely off all stone medications in 2023. The decrease in urine citrate while on topiramate did not seem to adversely affect her clinical stone formation nor her uric acid supersaturation.

To our knowledge, this is the first description of a non-alkaline-based, oral therapy used alone to dissolve uric acid stones. Although we emphasize some of the clinical challenges that arise when managing diet, obesity, and acid stones, it seems that further investigation of this class of medications in the setting of refractory uric acid nephrolithiasis is warranted. Perhaps a multipronged treatment strategy that comprehensively targets weight loss, insulin resistance, and urine pH while providing more patient-friendly medications may be the key to more effective and personalized UA disease therapies in the future.

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