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ORIGINAL ARTICLE

Medical dissolution therapy for the treatment of uric acid nephrolithiasis

Chad M. Gridley[1] · Michael W. Sourial[1] · Amy Lehman[2] · Bodo E. Knudsen[1]

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Abstract

Introduction Uric acid (UA) nephrolithiasis represents 10% of kidney stones in the US with low urine pH and high saturation of UA as the main risk factors for stone development. Dissolution therapy for UA kidney stones via urinary alkalization has been described as a treatment option. We present our experience in treating UA nephrolithiasis with medical dissolution therapy.

Methods A retrospective review was performed of UA stone patients referred for surgery but treated with dissolution therapy between July 2007 and July 2016. Patients were identified using ICD-9 codes. Patients were treated with potassium citrate alone or in combination with allopurinol. Serial imaging and urine pH were obtained at follow-up. Demographics, aggregate stone size, time to stone clearance, urine pH (office dip), and complications were recorded.

Results obtained Twenty-four patients (14 men and 10 women) were identified that started medical dissolution therapy for UA nephrolithiasis after initial referral for surgical management. Three patients (13%) did not tolerate the initiation of dissolution therapy and discontinued this treatment. Of the 21 patients that were maintained on dissolution therapy, 14 patients (67%) showed complete resolution of nephrolithiasis and 7 patients (33%) showed partial reduction. Patients with partial response had a mean reduction in stone burden of 68%. There were 3 recorded complications (UTI, GI upset with therapy, and throat irritation) and 4 recorded stone recurrences among these 21 patients.

Conclusion Based on our study population, medical dissolution therapy is a well-tolerated, non-invasive option for UA nephrolithiasis.

Keywords Uric acid · Nephrolithiasis · Dissolution · Alkalization

Abbreviations

AUA	American Urological Association
BMI	Body Mass Index
CT	Computed tomography
GI	Gastrointestinal
KUB	Kidney, ureter, and bladder X-ray
RUS	Renal ultrasound
SD	Standard deviation
UA	Uric acid
UTI	Urinary tract infection

Introduction

The incidence of stone disease in the US continues to rise with recent reports suggesting up to 1 in 11 people will develop a stone [1]. While most kidney stones have a calcium component, up to 12% of the patients will present with a uric acid (UA) component and nearly 10% of the stones are pure UA [2]. Uric acid kidney stone formation is dependent upon three urinary abnormalities: low urine pH, low urine volume, and elevated urine UA, with low urine pH the highest promoter of stone formation [3]. Several conditions have been associated with the formation of uric acid kidney stones including chronic diarrhea, myelo/lymphoproliferative disorders, malignancy, hemolytic disorders, high animal protein intake, gouty diathesis, and primary gout [3]. UA stone formation is also higher among patients with features of metabolic syndrome including diabetes mellitus type 2, obesity, and older age [4, 5].

✉ Bodo E. Knudsen
bodo.knudsen@osumc.edu

[1] Department of Urology, The Ohio State University Wexner Medical Center, 915 Olentangy River Road, Columbus, OH 43212, USA

[2] Center for Biostatistics, The Ohio State University, Columbus, OH, USA

The strong influence of urinary pH on UA stone formation may allow for dissolution therapy in some patients. Several studies have shown treatment efficacy in this manner, with 15–79% showing complete clearance of stone burden [6–8]. The aim of this study is to evaluate the rate of success in managing UA kidney stones with dissolution therapy institution in a group of patients referred to our tertiary care stone clinic for surgical therapy.

Patients and methods

Patient selection and evaluation

This was an institutional review board approved retrospective study. Charts of patients with renal or ureteric calculi between July 2007 and July 2016 were queried for pure uric acid stones or presumed uric acid stones (e.g., radiolucent stone on plain X-ray imaging, low-density on non-contrast CT scan, acidic urinary pH, etc.) for which there was initiation of a trial of dissolution therapy. Dissolution therapy consisted of oral potassium citrate alone or in combination with allopurinol. Potassium citrate dosing was typically started at 20 milli-equivalents (mEq) three times daily with meals and titrated as needed to achieve a urine pH of 6.5–7.0. On follow-up visit, if the urine pH remained < 6.5, the dose of potassium citrate was increased to 30 mEq three times daily with meals. Allopurinol dosing was 300 mg once daily. Patients with gout were told the importance of compliance with the daily Allopurinol, as missing doses could lead to a gout attack.

All the patients were treated and followed by one urologist (BK) with significant experience in the treatment of stones. Inclusion criteria included patients who presented with kidney stones visible on computed tomography and not visible on abdominal X-ray, kidney stones with Hounsfield units less than 500 on computed tomography, lack of acute renal colic, no evidence of obvious renal obstruction, urine pH less than 5.5, no contraindication to starting potassium citrate therapy, and patient agreeable to starting dissolution therapy. Of note, the patients were referred to our tertiary care center for surgical management of the stones. The concept of possible dissolution therapy was discussed at the initial consultation when it was identified that they may be candidates for such therapy.

Evaluation included a detailed medical and surgical history and physical exam, labs, and urinalysis (Siemens Clinitek Status+ Analyzer, Siemens Medical Solutions USA, Malvern, PA, USA). Imaging included a baseline plain abdominal X-ray and computed tomography (CT) scan or renal ultrasound (RUS). Follow-up visits were typically within 1–3 months to assess for initial response, then periodically afterwards according to surgeon's discretion. At each visit, response to dissolution therapy was measured by radiological imaging (either CT or RUS) and tolerability was assessed. Patients were given the option to undergo surgical intervention where indicated.

Data

Demographic characteristics (age, BMI, history of prior stones, diabetes, gout, and malignancy) were obtained from the patients' charts. Imaging characteristics (radiolucency on KUB, stone location, laterality, largest stone diameter, total stone burden on CT or RUS pre- and post-treatment), medication(s) used for dissolution therapy, adverse events, length of therapy, and urine pH pre- and post-treatment were abstracted from the data. Target urinary pH was defined as > 6.0 [1]. Complete stone clearance was defined as no residual stones or punctate stones (1–2 mm) on imaging. Partial stone clearance was defined as reduction in total stone burden yet persistence of kidney stones on follow-up imaging.

Endpoints

The primary objective was to report the efficacy of medical dissolution therapy via reduction in stone burden on radiographic imaging. Secondary objectives were to report the response of therapy via urinary pH as well as the safety and tolerability of medical dissolution therapy.

Statistics

Descriptive statistics were used to characterize the clinical characteristics (both overall and by response group) and outcomes of the study cohort. Continuous variables were reported as means (standard deviations) with ranges; due to skewness, time variables (e.g., months of therapy) were reported as medians (25th and 75th percentiles) with ranges instead. Categorical variables were described with proportions. All analyses were performed using SAS/STAT software, version 9.4 of the SAS system for Windows (SAS Institute, Inc., Cary, NC, USA).

Results

Twenty-four patients (10 females and 14 males) were started on medical dissolution therapy between July 2007 and July 2016 at our institution. Three patients (13%) had stopped dissolution therapy upon their first follow-up visit. Reasons for this included prohibitive cost, gastrointestinal symptoms, and elevated creatinine. The remaining 21 patients were maintained on dissolution therapy. An additional three patients (13%) underwent surgical intervention during their

dissolution course. One patient showed response to dissolution therapy but underwent ureteroscopy at their discretion following discussion with the surgeon. The second patient was started on dissolution therapy, underwent ureteroscopy at their request following discussion with the surgeon, and went on to have reduction of the residual stone burden while maintained on potassium citrate. The third patient developed a urinary tract infection during dissolution therapy that required hospitalization, and a decision to proceed with surgical management of the stone was made after treatment of the acute infection. Demographic characteristics of the 21 patients on dissolution therapy are shown in Table 1. Overall, the mean age at presentation was 55.8 years [standard deviation (SD) = 8.8 years] and mean BMI was 43.7 (SD = 12.9). Two patients (10%) had a history of gout. Twelve patients (50%) had a documented serum uric acid level drawn at the initiation of dissolution therapy and of these, eight had an elevated level (> 7.0 mg/dL). Three patients (14%) had a history of malignancy (uterine, thyroid, and colon). Thirteen patients (62%) had a history of diabetes mellitus: 57% (8/14) of complete responders and 71% (5/7) of partial responders. Fifteen patients (71%) reported a previous history of uric acid nephrolithiasis. Mean aggregate stone burden at presentation was 30.9 mm (SD = 17.9 mm), and was higher in the partial responders compared to complete responders (41.9 mm vs. 25.4, respectively). The mean Hounsfield unit measurement was 403.9 (SD = 121.7), and mean urinary pH at presentation was 5.4 (SD = 0.4). Twenty patients (95%) had radiolucent stones on X-ray; 3 (14%) were faint. All 21 patients were started on potassium citrate therapy, and 16 patients (76%) were also started on allopurinol.

Imaging characteristics are listed in Table 2. All patients received at least one CT scan during follow-up. Among the seven partial responders, the median number of CT scans during follow-up was 1 (25th, 75th percentile: 1, 3 scans). For 14 complete responders, the median number of CT scans was 2 (25th, 75th percentile: 1, 2 scans). Timing of CT scan ranged from 0.1 months to a maximum 7.2 months. In addition to CT scans, 3/7 (43%) of partial responders and 10/14 (71%) of complete responders received at least 1 ultrasound. Two of the three partial responders received one ultrasound, and the third partial responder received five. Among the ten complete responders with at least one RUS, the median number of RUS was 1.5 (25th, 75th percentile: 1, 3 ultrasounds). Timing of RUS ranged from 0.2 months up to 9.1 months.

A summary of the response to therapy for the 21 patients maintained on dissolution therapy is shown in Table 3. Fourteen patients (67%) had complete stone clearance during follow-up; for these patients, the median time to clearance was 3 months (25th, 75th percentile: 2, 9 months). An example of this is provided in Fig. 1. In particular, nine patients (42.9%) had cleared their stone burden by their first follow-up appointment (median time = 2 months; 25th, 75th percentile: 2, 3 months). Seven patients (33%) showed partial clearance and on average reduced their aggregate stone burden by 68% (mean reduction in size = 28 mm, SD = 9.9 mm). Of these seven individuals, abdominal X-ray at presentation showed faint or radio-opaque calcifications in three individuals.

Overall, urine pH was raised to a mean of 6.3 (SD = 0.9) on urine dip at first follow-up with variable timing since last dose of potassium citrate (Table 2). Throughout their respective treatment courses, 16/21 patients (76%) were recorded as having reached this goal pH on office urinalysis on at least one visit; 12 patients reached the target urinary pH > 6.0 on their first follow-up visit.

Out of the 21 patients on dissolution therapy, there were three recorded complications (UTI, GI upset, and throat irritation). There were four recorded stone recurrences ranging in size from 3 mm to 12 mm. The 12-mm stone was cleared with resumption of oral dissolution therapy while the other three recurrences were monitored with observation.

Discussion

UA stone formers are a small subset within the North American kidney stone forming population and possess unique management strategies that are described within the American Urological Association (AUA) Guidelines on the medical management of kidney stones [1]. In addition to the recommendation for all stone formers to increase fluid intake to achieve 2.5 L of urine production daily, specific dietary recommendations for UA stone formers include limiting non-dairy animal protein, particularly avoiding "high purine" foods containing > 150 mg, and increasing the alkali renal load primarily from fruits and vegetables. It is important to discuss dietary changes with patients as the most common reason for hyperuricosuria on 24-h purine collection is purine gluttony [9]. Pharmacological therapies include urinary alkalization to increase the urine pH to 6.0, with potassium citrate the most commonly utilized alkali agent. It has also been suggested to raise the urine pH to 7.0 for treatment and 6.5 for prevention of uric acid stones [10]. Raising the urine pH above 7.0 is not recommended as this may increase the risk of calcium phosphate stone formation [11].

Other alkali agents such as sodium bicarbonate or sodium citrate can be considered in patients at risk of hyperkalemia. Tung et al. [12] described 100% success with oral sodium bicarbonate urinary alkalization in eight patients. Sodium bicarbonate carries an increased risk of calcium stone formation due to the sodium load. Alternatively, it has been suggested to combine potassium citrate with sodium citrate in patients with renal insufficiency to achieve urine alkalization while reducing the risk of hyperkalemia [11]. Furthermore,

Table 1 Demographic characteristics of patients on dissolution therapy

Characteristic	Level	Complete responders ($n=14$)	Partial responders ($n=7$)	Total ($n=21$)
Sex	Male	10 (71%)	3 (43%)	13
	Female	4 (29%)	4 (57%)	8
Age	Mean (SD) (range)	($n=14$) 55.4 (10.2) (42–70)	($n=7$) 56.6 (5.8) (52–69)	($n=21$) 55.8 (8.8) (42–70)
BMI	Mean (SD) (range)	($n=14$) 41.1 (13.2) (23.9–64.2)	($n=7$) 48.8 (11.7) (32.7–69.8)	($n=21$) 43.7 (12.9) (23.9–69.8)
History of gout	No	12 (86%)	7 (100%)	19
	Yes	2 (14%)	0	2
History of malignancy	No	13 (93%)	5 (71%)	18
	Yes	1 (7%)	2 (29%)	3
History of diabetes	No	6 (43%)	2 (29%)	8
	Yes	8 (57%)	5 (71%)	13
History of previous uric acid stone	No	2 (14%)	0	2
	Yes	9 (64%)	6 (86%)	15
	Possible	3 (21%)	1 (14%)	4
Radiolucent on KUB?	No	0	1 (14%)	1
	Yes	13 (93%)	4 (57%)	17
	Faint	1 (7%)	2 (29%)	3
Total stone burden (mm)	Mean (SD) (range)	($n=14$) 25.4 (17.4) (8–66)	($n=7$) 41.9 (14.4) (21–64)	($n=21$) 30.9 (17.9) (8–66)
Stone location	Kidney	8 (57%)	5 (71%)	13
	Ureter	2 (14%)	0	2
	Kidney, ureter	4 (29%)	2 (29%)	6
Hounsfield unit	Mean (SD) (range)	($n=14$) 392.1 (139.9) (139–649)	($n=6$) 431.3 (63.8) (323–488)	($n=20$) 403.9 (121.7) (139–649)
Stone laterality	Left	5 (36%)	2 (29%)	7
	Right	8 (57%)	2 (29%)	10
	Bilateral	1 (7%)	3 (43%)	4
Stented?	No	10 (71%)	4 (57%)	14
	Yes	4 (29%)	3 (43%)	7
Pretreatment urinalysis pH	Mean (SD) (range)	($n=13$) 5.5 (0.4) (5–6.5)	($n=6$) 5.3 (0.3) (5–5.5)	($n=19$) 5.4 (0.4) (5–6.5)
Serum uric acid	Mean (SD) (range)	($n=9$) 7.5 (1.7) (5.2–10.5)	($n=3$) 8.1 (1.2) (7.2–9.4)	($n=12$) 7.6 (1.5) (5.2–10.5)
Potassium citrate (final dose after adjustment)	20 mEq TID	7 (50%)	3 (43%)	10
	30 mEq BID	2 (14%)	1 (14%)	3
	30 mEq TID	5 (36%)	3 (43%)	8
Allopurinol	Missing	3 (21%)	2 (29%)	5
	100 mg QD	2 (14%)	1 (14%)	3
	300 mg QD	9 (64%)	4 (57%)	13

due to the increased sodium load, sodium bicarbonate therapy carries increased risk for patients with congestive heart failure, liver cirrhosis, and uncontrolled hypertension [13]. In addition, monosodium urate is less soluble in urine than monopotassium urate [9]. In patients unable to raise urine pH over 6.5 with potassium citrate therapy alone, acetazolamide has been used as an adjunct to increase urinary pH as it leads to an increased production of urinary bicarbonate

Table 2 Imaging characteristics of patients on dissolution therapy

Response	Total patients	Procedure	Number of patients with procedure (%)	Number of scans per patient (among those with scan): median (Q1, Q3) (min, max)	Month of CT scan or US (min, max)
Partial	7	CT	7 (100%)	1 (1,3) (1, 4)	(0.1, 3)
		US	3 (43%)	1 (1, 5) (1, 5)	(0.6, 5.3)
Complete	14	CT	14 (100%)	2 (1,2) (1, 7)	(0.1, 7.2)
		US	10 (71%)	1.5 (1, 3) (1, 6)	(0.2, 9.1)

Table 3 Response to dissolution therapy

Characteristic	Level	Complete responders ($n=14$)	Partial responders ($n=7$)	Total ($n=21$)
Total length of dissolution therapy (months)[a]	Median (IQR) (range)	($n=14$) 15.5 (10, 37) (2, 72)	($n=7$) 22 (8, 44) (5, 53)	($n=21$) 20 (10, 37) (2, 72)
Urine pH at first follow-up	Mean (SD) (range)	($n=12$) 6.1 (0.8) (5, 7)	($n=7$) 6.8 (0.9) (5, 7)	($n=19$) 6.3 (0.9) (5, 7)
Time of first follow-up (months)	Median (IQR) (range)	($n=12$) 2 (1.8, 3) (1, 6)	($n=7$) 2 (1, 4) (1, 4)	($n=19$) 2 (1.5, 3) (1, 6)
Urine pH at time of last stone measurement[b]	Mean (SD) (range)	($n=12$) 6.2 (0.9) (5, 7.5)	($n=5$) 6.5 (0.9) (5.5, 7.5)	($n=17$) 6.3 (0.9) (5, 7.5)
Urine pH > 6 at least once during follow-up	No	5 (43%)	0	5
	Yes	9 (64%)	7 (100%)	16
Time of last stone measurement (months)	Median (25th, 75th percentile) (range)	($n=14$) 3 (2, 9) (1, 23)	($n=7$) 8 (4, 30) (1, 53)	($n=21$) 4 (2, 10) (1, 53)
Complications	No	11 (79%)	7 (100%)	19
	Yes	3 (21%)	0	2
UA stone recurrence	Missing/NA	0	6 (86%)	6
	No	10 (71%)	1 (14%)	11
	Yes	4 (29%)	0	4

[a]Until last follow-up

[b]For patients 6 and 15, the urine pH is from the following month; there was no corresponding urine pH at the time of their last stone measurement

[11, 13]. Its use should be closely monitored though as it can reduce urinary citrate and increase urinary calcium [9]. We did not use sodium bicarbonate, sodium citrate, or acetazolamide in this series of patients.

Allopurinol is typically not offered as first-line therapy but may be considered as an adjunct when alkalization is not successful or for patients who continue to form uric acid stones despite adequate alkalization of the urine. For patients with a history of gout, or with elevated levels of serum uric acid, there may also be value in allopurinol therapy. It is the practice of the authors to provide allopurinol when actively treating patients with oral dissolution therapy. Following successful treatment, the allopurinol is stopped and the patient is maintained on preventative potassium citrate.

Reports within the literature describing outcomes of dissolution therapy span several decades. In 1977, Petritsch reported his series of 140 patients who were treated with oral dissolution therapy for presumed uric

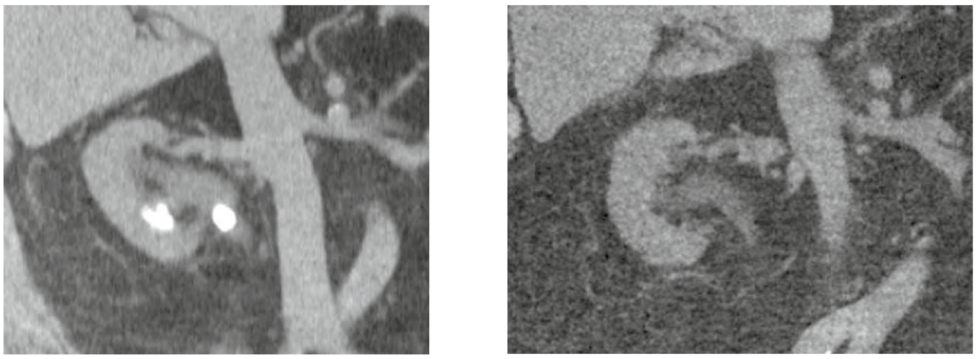

Fig. 1 Patient 3: 20 mm stone × 2 (pictured), 66 mm aggregate. Complete resolution at 2 months. **a** Presentation, pH 5.5. **b** 2 months, pH 7.0

acid kidney stones using potassium sodium hydrogen citrate [8]. He described an 80% success rate with success being defined as stone clearance on intravenous pyelogram. More recently, Sinha et al. [6] described their experience with managing radiolucent kidney stones with urinary dissolution therapy. The authors performed a retrospective review of patients believed to have uric acid urolithiasis that were managed with oral potassium magnesium citrate. In their population of 67 patients, 15% experienced complete dissolution and 19% experienced total stone burden dissolution greater than 50% as seen on ultrasound. Neither of the two studies described utilized computed tomography to define initial stone burden nor confirm clearance during therapy.

Our contemporary results compare very favorably to series reported in the literature. In our population, therapy was well-tolerated with only three patients discontinuing therapy. Our study suggests that even with substantially large stone burden, complete clearance of uric acid stones is achievable in two-thirds of our patients, with some patients completely clearing their stones as early as the first follow-up visit and confirmed with CT. Additionally, 30% of our population showed a response to urinary alkalization, experiencing a 68% reduction in their aggregate stone burden, which can either change or facilitate future planned surgical intervention. Of all the partial responders, stone analysis was available for five of the seven patients. Four of these five had a stone analysis that showed 100% UA composition and one patient had mixed stone composition (80% uric acid and 20% calcium oxalate dihydrate). Reasons for incomplete stone clearance within the partial responder group could be explained by heterogeneous stone composition or partial/non-compliance with medication usage. For those who eventually went on to have surgical intervention for stone management, the reduction in stone burden may have facilitated the surgical procedure.

Risks exist for any treatment strategy including dissolution therapy. One concern is whether a patient may develop an acute episode of colic from a stone moving into the ureter as it is reduced in size during the dissolution process. Interestingly, we did not have any of our patients present with acute colic during the dissolution phase of their therapy. However, we recommend discussing this potential risk for all patients embarking on therapy.

The administration of potassium citrate carries with it the risk of hyperkalemia. Patients should be screened for renal dysfunction prior to starting potassium citrate therapy. Renal function and serum potassium should be periodically monitored during treatment. One patient within our study did develop a urinary tract infection requiring hospitalization. It is unknown if the patient's stone history played a part during this admission, but surgical stone management was undertaken to remove a potential source of infection.

There are several limitations to our study, including a small sample size and its retrospective nature. Additionally, the timing of follow-up visits and imaging modalities used were not standardized, and thus varied somewhat amongst the patients. We provide verbal and written dietary recommendations to all stone patients in our practice, but adherence to those recommendations may be confounding our results. The urine pH of the patients was checked in the office and the patients questioned about compliance with the medications, but a formal mechanism such as pill counting to ensure compliance was not in place and, therefore, could have been a factor in non- and partial responders. The cost-effectiveness of this intervention was also not measured but given that the majority of the patients were referred for surgical management, and given the high cost of surgical intervention, it would seem intuitive that medical dissolution therapy, if successful, would provide a cost-effective option for this patient population. To our knowledge, this is the largest contemporary single-center series utilizing

CT imaging to evaluate medical dissolution therapy alone to treat uric acid stones, and confirm its efficacy and tolerability in treating significant stone burden. Future studies should address specific costs of medical dissolution therapy compared to surgical intervention and include quality of life metrics such as the Wisconsin Stone Quality of Life Metric [14].

Conclusion

Medical dissolution therapy for presumed UA urolithiasis appears to be well tolerated in our study population, carries a high stone clearance rate, and potentially avoids the morbidity of surgical intervention.

Author contributions CMG data collection, manuscript writing and editing. MWS data collection and manuscript editing. AL data analysis and manuscript editing. BEK study design, project development, and manuscript editing.

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Compliance with ethical standards

Conflict of interest Bodo Knudsen is a consultant for Olympus Surgical, Boston Scientific, Thermedx, and Bard Medical. The remaining authors have no disclosures

Ethical approval The study was approved by the Ohio State University Office of Responsible Research Practices Institutional Review Board (IRB) and conducted in accordance with this. Patient consent was waived by the IRB given the retrospective study design.

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