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ORIGINAL PAPER

Cystone® for 1 year did not change urine chemistry or decrease stone burden in cystine stone formers

Stephen B. Erickson · Terri J. Vrtiska · Vincent J. Canzanello · John C. Lieske

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Abstract Cystine kidney stones frequently recur because inadequate prevention exists. We recruited documented recurrent cystine kidney stone formers (6 men, 4 women, 44 ± 17 years) into a 2-phased study to assess safety and effectiveness of Cystone®, a herbal treatment used to prevent and facilitate passage of cystine kidney stones. The first phase was a randomized double-blinded 12 weeks crossover study assessing the effect of Cystone® versus placebo (2 tablets BID) on urinary chemistries. The second phase was an open label 1 year study of Cystone® to determine if renal stone burden decreased, as assessed by quantitative and subjective assessment of CT. There was no statistically significant change of urinary composition from baseline short (6 weeks) or long (52 weeks) term on Cystone®, including volume (2,525, 2,611, 2,730 ml), pH (6.7, 6.7, 7.05), and cystine excretion (2,770, 2,889, 4,025 µmol). Pre and post-CT was available in nine patients. Although seven kidneys lost stones spontaneously or surgically, overall stone burden increased in seven kidneys, was unchanged in nine, and fell in only two. Quantitative scoring increased in both the left and right kidneys (1,602–1667 and 301–2,064 volumetric units, respectively). Therefore, this study does not suggest that Cystone® has a favorable effect on urinary chemistries that could decrease cystine stone formation, nor does it appear to prevent stone growth or promote stone passage over a 1-year period.

Keywords Computerized tomography · Cystone® · Herb · Kidney calculi · Supersaturation · Nephrolithiasis · Quantitative CT

Abbreviations

AU	Agatston units
CT	Computerized tomography
GI	Gastrointestinal
mm^3	Cubic millimeter

Introduction

Cystine kidney stones are uncommon, accounting for about 1% of all stone formers and occur in patients with the autosomal recessive disorder, cystinuria. Cystine stones are especially prone to recur because cystine is poorly soluble in urine of usual pH and volume, and because prevention programs are difficult to follow. Cystinuria is caused by mutation of the dibasic amino acid transporter, either in its heavy chain, known as rBAT [1] or in its light chain known as bo,+A [2]. Current prevention strategies include enough oral fluid to excrete over 3 l of urine per day, a diet low in protein and sodium, urinary alkalinization to a pH over 7.0 and cysteine chelators to prevent the formation of the insoluble cysteine dimer, cystine [3–10]. No new treatments

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S. B. Erickson (✉) · V. J. Canzanello · J. C. Lieske
Division of Nephrology and Hypertension,
Department of Laboratory Medicine and Pathology,
Mayo Clinic, 200 First Street S.W., Rochester, MN 55905, USA
e-mail: erickson.stephen@mayo.edu

V. J. Canzanello
e-mail: vcanzanello@mayo.edu

J. C. Lieske
e-mail: lieske.john@mayo.edu

T. J. Vrtiska
Department of Diagnostic Radiology, Mayo Clinic,
200 First Street S.W., Rochester, MN 55905, USA
e-mail: vrtiska.terri@mayo.edu

have been established in decades, and those that are available have inherent problems related to patient compliance, cost, effectiveness and drug side effects. Therefore, a preventive treatment that would be easy to take, low in cost, safe and effective would be highly desirable.

With investigator-initiated partial funding and provision of Cystone® from Himalaya Health Care, this study was performed.

Cystone® tablets are an ayurvedic treatment for stones, traditionally practiced in India, and represents a candidate for further investigation (http://himalayahealthcare.com/aboutayurveda/himalaya.htm). One of the authors met a patient who had experienced a nearly miraculous "cure" of cystine stone formation. By his early teens, this patient had had a unilateral nephrectomy because of cystine stone complications and had multiple operations including placement of a chronic nephrostomy tube in the other. Following regular Cystone® use, this patient experienced no further stones over 30 years. Many studies and long experience attest to the safety of this compound (http://himalayahealthcare.com/researchpaper/cystone.htm). It is claimed by the manufacturer that Cystone® decreases urinary supersaturation or micropulverizes and expels kidney stones, but existing studies have been limited by small patient numbers, weak methodology, and poor study design including lack of proper controls (http://himalayahealthcare.com/researchpaper/cystone.htm). Therefore, in this study we rigorously evaluated the ability of Cystone® to decrease urine determinants of cystine stone formation and to prevent new stone formation and growth of existing stones. Quantitative computerized tomography (CT) was used to assess changes in stone burden over the time of the study.

Materials and methods

Study subjects

The study was approved by the Mayo Clinic Institutional Review Board. All subjects provided written informed consent. Ten adult patients (6 men, 4 women) with recurrent, analytically confirmed, cystine kidney stones were recruited from the Mayo Stone Clinic. All were Caucasian adults and had passed at least one stone at entry into the study (Table 1). Metabolic activity prior to study entry was defined as an increase in stone size or number documented on a previous CT scan obtained within 1 year prior to study entry. Five patients were metabolically active at entry into the study; two were metabolically indeterminate. Exclusions included age under 18 years, pregnancy, refusal to use an effective method of birth control during the study, chronic urinary infection or mental incompetence to give informed written consent on a form approved by the institutional review board. All patients were allowed to continue their existing kidney stone treatment programs.

Study design and conduct

The protocol is illustrated in Fig. 1. Patients were randomly assigned by the Mayo Clinic Research Pharmacy to a

Table 1 Patient characteristics

Patient number	Age	Gender	Race	Stone activity at entry	Concomitant treatment	Miscellaneous
1	49	Male	W	Yes	Potassium citrate 60 mEq/day	Stone passages
					Captopril 150 mg/day	L ESWL @UPJ
2	52	Female	W	No	Potassium citrate 60 mEq/day→DC	No stone passages
					Captopril 75 mg/day	4 UTI
3	74	Male	W	No	D-Pen 750 mg/day→Thiola 800 mg/day	Left stone passages
					Potassium citrate 45 mEq/day→210 mEq/day	
4	26	Male	W	Yes	Potassium citrate 60/day	L perc × 2
					D-Pen 1,500 mg/day	L stone passages
5	42	Male	H	Yes	Potassium citrate 45 mEq/day	No stone passages
					Thiola 800/day	
6	24	Female	W	Unknown	Potassium citrate 45 mEq/day	Dropped out after 6 weeks
7	40	Female	W	Yes	Potassium citrate (sliding scale)	R stone basket extraction
8	54	Male	W	Yes	Potassium citrate 20 mEq/day	L stone passages but better on Cystone®
9	58	Male	W	No	D-Pen 2,000 mg/day	Did not return for final visit
10	19	Female	W	Unknown	Thiola 1,000 mg/day	L ureteroscopic lithotripsy
					Potassium citrate sliding scale	

W white, *H* Hispanic, *L* left, *R* right, d-*Pen* D-penicillamine, *UTI* urinary tract infection, *Perc* percutaneous lithotripsy, *ESWL* extracorporeal lithotripsy, *UPJ* ureteropelvic junction, *DC* Discontinued

STUDY PROTOCOL

START	CROSSOVER PERIOD					OPEN LABEL EXTENSION	
	6 weeks		1 week	6 weeks		46 weeks	END
Urine supersaturation x 2 Renal CT	Cystone	Urine supersaturation x 2	washout	Placebo	Urine Supersaturation x 2	Cystone	Urine supersaturation x 2 Renal CT
	Placebo	Urine supersaturation x 2	washout	Cystone	Urine Supersaturation x 2	Cystone	

Fig. 1 Study protocol

6-week treatment program with Cystone® tablets, two by mouth twice daily, or identical placebo. This is the dose recommended by the manufacturer. After a 1 week washout the patients crossed over to the alternate treatment for another 6 weeks. Patients provided two 24-h urine collections shortly before starting the study, at the end of the first 6 weeks of treatment, and again at the end of the 6 weeks crossover, each of which were analyzed for sodium, pH, cystine and volume in the Mayo Renal Function Laboratory. After completing both crossover arms, patients then immediately took Cystone® open label in the same dose for an additional 48 weeks, thus ensuring a 52-week total exposure to Cystone® during the 59-week study.

Quantitative noncontrast multidetector CT exams were all performed on a 64-channel MDCT scanner (Sensation-64, Siemens Medical Solutions, Forcheim, Germany). A standardized acquisition protocol was used for all exams [collimation 64 × 0.6; gantry rotation time, 0.5 s; table feed, 23 mm/rotation (pitch of 1.2), quality reference 240 mAs; 120 kVp and the field of view was adjusted to patient size]. Three reconstruction intervals were obtained from the raw data including: 5.0 mm thickness at 5.0 mm intervals (axial), 2.0 mm thickness at 2.0 mm intervals (axial) and 2.0 mm thickness at 2.0 intervals (coronal adjusted to the long axis of the kidneys). The 2.0 mm thickness at 2.0 mm interval (axial) data set was also processed at a free standing 3D workstation (Vitrea, Vital Images, Inc., Minnetonka, MN) by dedicated 3D technologists to obtain quantitative scoring data for each kidney. Scored images were reviewed to determine that the included opacities were consistent with urolithiasis rather than renal arterial or parenchymal calcifications. The scoring programs are typically used for coronary artery calcification quantification and generate both an Agatston score (reported as Agatston Units, AU) and volumetric score (reported as mm^3). In the algorithms positive calcification required a minimum density threshold of 130 Hounsfield Units and a minimum area threshold of 3 adjacent pixels of at least 130 Hounsfield Units. In addition to quantified scoring, all images including the axial and reconstructed coronal series were reviewed by the diagnostic radiology service and a clinical report was generated. These images were subsequently sent to a picture archiving and communication system and available for referring clinicians. Additional details are available in a previous publication [11]. All images were reviewed by a radiologist (T.J.V.) in a blinded fashion to score each kidney as increased, no change, or decreased stone burden.

Currently, the method of choice for imaging renal stones has been nonenhanced CT with accuracies in the depiction of the size and location of renal calculi approaching 100% using current CT technology which is more accurate than either renal ultrasound or KUB with tomography. However, an important consideration of CT acquisition is limiting radiation exposures. Fortunately, advances in CT imaging, in general, have allowed CT images to be acquired using radiation doses that are typically 40–50% lower than earlier CT scanner acquisitions by limiting the coverage area (*z*-axis) of the scan acquisition and adjusting the tube current (automated mA modulation) based on patient size. Both appropriate *z*-axis coverage (kidneys alone vs. kidneys through bladder) and automated mA modulation were used for all CT exams in this study.

Study drug

Cystone® is traditionally used for relief of a variety of urological problems including nephrolithiasis and is comprised of the following substances: shilapuspha (*Didymocarpus pedicellata*) 130 mg, Pasanabheda (*Saxifraga ligulata* Syn. *Bergenia ligulata/ciliata*) 98 mg, Manjishtha (*Rubia cordifolia*) 32 mg, Nagarmusta (*Cyperus scariosus*) 32 mg, Apamarga (*Achyranthes aspera*) 32 mg, Gohija (*Onosma bracteatum*) 32 mg, Sahadevi (*Vernonia cinerea*) 32 mg, Shilajeet (Purified) 26 mg, and Hajrul yahood bhasma 32 mg (http://himalayahealthcare.com/products/cystone.htm#f). Its purported effect is to "prevent supersaturation of lithogenic substances, control oxamide (a substance that precipitates stone formation) from the intestine and correct the crystalloid–colloid imbalance. Cystone® inhibits calculogenesis by reducing stone-forming substances like oxalic acid, calcium hydroxyproline, etc., and causes their expulsion by micropulverization. Cystone® causes disintegration of the calculi and crystals by acting on the mucin, which binds the particles together. Cystone®'s antimicrobial activity is beneficial in the prevention of urinary tract infections

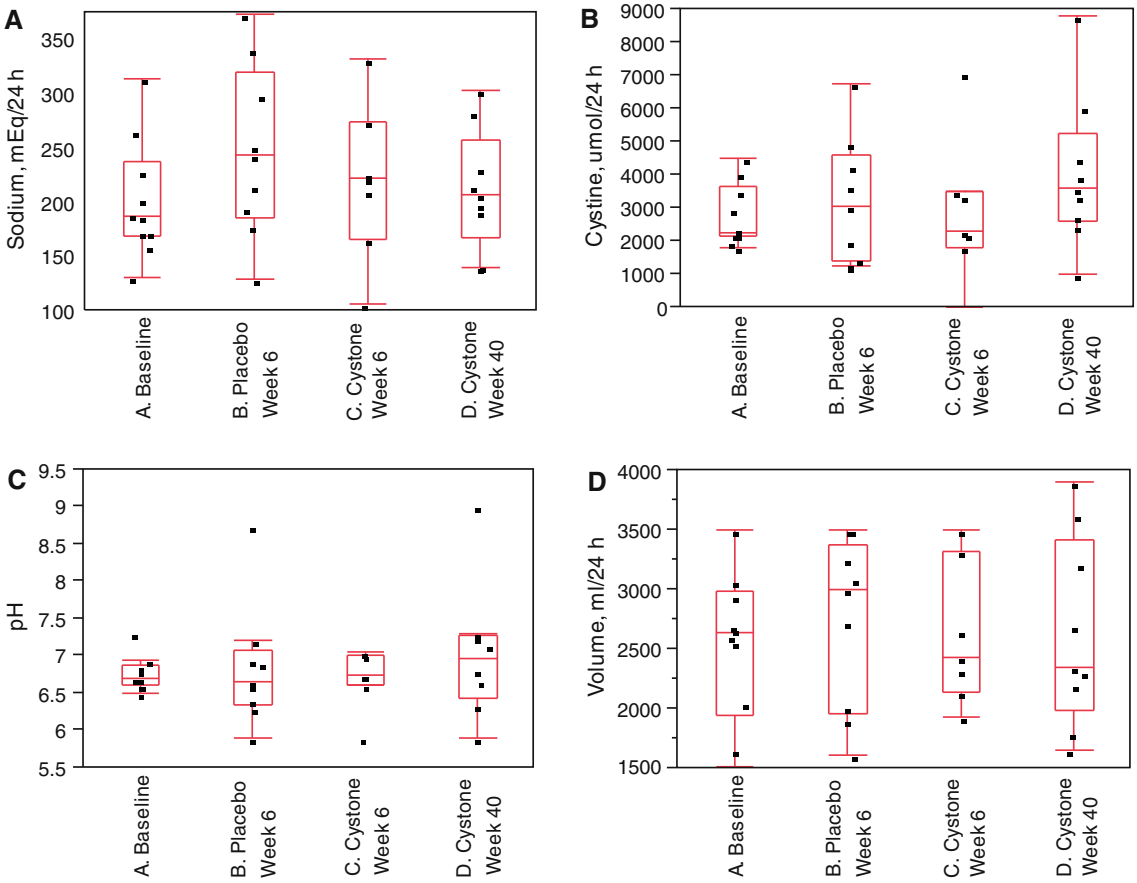

Fig. 2 Urine chemistries

associated with urinary stones and crystalluria. Cystone®'s antispasmodic and anti-inflammatory activities relieve ureteric colic and alleviate symptoms of painful and burning and micturition." (http://himalayahealthcare.com/products/cystone.htm). Cystone® is manufactured and sold virtually world wide by Himalaya Health Care. In the United States, the product is known as Uricare®.

Statistics and randomization

Randomization was accomplished using a table provided by the Division of Biostatistics to the Mayo Research Pharmacy. The study coordinator and investigators were blinded as to whether the patients received placebo or Cystone®. Biochemical and supersaturation results were analyzed via a matched pair analysis using the JMP software package (SAS Instituted, Inc.); P values <0.05 were deemed significant.

Results

Table 1 contains demographic and clinical characteristics of the study patients that included six men and four women (44 ± 17 years). Patients who consented to participate in the Cystone® study had multiple recurrent kidney stones inadequately controlled on their current program. This tended to select a more difficult-to-treat patient population. Three patients thought that Cystone® could be discriminated from placebo by its "peppery" taste. The other study participants did not identify this difference.

Figure 2 displays the 24 h urinary chemistry results. In a matched pair analysis of the initial crossover study, no statistically significant differences for any parameter between Cystone® treatment as compared to placebo were present. Similarly, the 24-h urine chemistries did not differ after 1 year on Cystone® as compared to values on placebo during the initial crossover period. A possible exception is a drop in urine sodium ($P = 0.045$) at the end of the study. We have no physiologic explanation for this and it may therefore represent a type 2 statistical error due to multiple comparisons. Overall there was no evidence that Cystone® altered urinary chemistries after short-term (6 weeks) or long-term (1 year) usage.

Table 2 contains results of CT studies at baseline and 1 year. The blinded radiologist's opinion of changes in kidney stone burden agreed with the quantitative data. Patient 6 was excluded from CT analysis because she did not return for a final CT. Therefore, we evaluated 18 of 20 kidneys for

Table 2 CT scores

Patient	Baseline volume	Baseline Agatston	1-year volume	1-year Agatston	Radiologist impression	Clinical events
Right kidneys						
1-001	3,494	4,564	4,078	5,286	NC	None
1-003	13	11	8	5	NC	None
1-004	0	0	0	0	NC	None
1-006	0	0	19	6	NC	None
1-007	9,955	13,187	9,211	12,221	NC	None
1-009	29	28	130	144	I	None
1-011	21	14	19	17	NC	None
1-012	914	1,167	1,631	1,974	I	None
1-014	0	0	0	0	NC	None
Mean	1,602	2,107	1,677	2,183		
SD	3,335	4,417	3,139	4,157		
P vs. baseline			0.96	0.97		
Left kidneys						
1-001	71	64	2,673	3,484	I	SURG
1-003	0	0	0	0	NC	None
1-004	83	105	88	109	NC	PASS
1-006	310	380	1,086	1,407	I	PASS + SURG
1-007	260	331	6,305	8,390	I	None
1-009	95	92	64	50	D	SURG
1-011	31	31	235	299	I	PASS
1-012	1,333	1,755	1,901	2,138	I	?
1-014	530	688	282	332	D	SURG
Mean	301	383	2,064	1,801		
SE	422	560	688	2,741		
P vs. baseline			0.13	0.15		

I increased stones, *D* decreased stones, *NC* no change in stones, *PASS* passed stone, *SURG* stone removed, ? unknown

stone burden. Spontaneous stone passage occurred from 2 of 18 kidneys during the study. An additional four kidneys required a surgical procedure to remove stones. One kidney lost stone material both by spontaneous passage and surgery. In all, seven kidneys lost documented stones. Nevertheless, the official radiology interpretation was that seven kidneys had increased stone material, nine kidneys were unchanged, and only two kidneys had decreased stone material. Quantitative scoring of renal stone content in 18 kidneys from these same 9 patients revealed that mean total stone burden per right kidney remained stable during this time period as assessed by the volumetric scoring system (1,602–1,677 mm^3; $P = 0.96$ by matched pairs analysis) or the Agatston scoring system (2,107–2,183 AU; $P = 0.97$ by matched pairs analysis). Mean total stone burden per left kidney changed by volumetric scoring from 301 to 2,064 mm^3; $P = 0.13$ by matched pairs analysis and by the Agatston scoring system from 383 to 1,801 AU; $P = 0.15$ by matched pairs analysis. These results did not support an overall positive effect of Cystone® on stone burden.

No patients described any side effects attributable to Cystone®, consistent with previous studies.

Discussion

Current non-surgical therapies of cystine stones take three different approaches. Prevention is preferred. Although no randomized trials exist, measures to increase urinary dilution, decrease urinary excretion of cystine and increase urinary solubility of cystine are rational approaches. To this end, hydration therapy, diets low in sodium [3, 4] and protein [5], cysteine chelators [6, 7], and urinary alkalinization [8] are all in clinical use. Hydration therapy is inconvenient. In order to be effective a low methionine diet must be very low in protein and is therefore difficult to follow and tasteless. Chelators are expensive and have a high rate of discontinuation due to rash, bone marrow suppression, proteinuria and GI intolerance [9, 10]. Urinary alkalinizers are ineffective unless the urine pH is maintained above 7.0 [8],

requiring frequent and large doses, often accompanied by GI side effects. Clinical experience has shown that chemolysis can occur when the prevention program is followed optimally [12]. However, drug compliance is often poor. Expulsion therapy to help pass stones that have moved into the ureter is supported by controlled trials [13, 14].

Several herbs have been purported to decrease stone formation, break up existing stones, or hasten stone passage. However, rigorous scientific evidence confirming efficacy is lacking. Some examples include the Chinese Kampou medicine, including the species Takusya and Kagosou [15, 16]. Chorey-to, another Chinese medicine which contains Takusya [17], and the Brazil tea made from the annual herb *Phyllanthus niruri* termed "break stone" [15, 17] which contains such potentially active compounds as alkaloids, flavonoids, lactones, steroids, terpenoids, lignans, and tannins. The Moroccan herb *Hernaria hirsuta* is purported to act by promoting nucleation of more crystals that achieve a smaller size and has been evaluated previously by our group [18]. We have also previously investigated the effects of Cystone® in calcium oxalate stone formers and found no effect on urine chemistries or stone formation rate over 1 year [11].

Clinical trials to prevent kidney stones have been traditionally hindered by the lack of valid endpoints. Typically, the number of stone passages before and after the intervention serve as the measure of success. There are two major issues that invalidate this methodology. First, patients may be motivated to seek stone prevention following a particularly severe colic or increased frequency of colics. The improvement after treatment may be confounded by regression to the mean. The second problem is the assumption that stones pass shortly after formation. However, the time between stone formation and passage appears variable and unpredictable. No current stone prevention strategies claim to prevent stone passage. They claim to prevent stone formation and growth. Therefore, we used a combined end point in this study, stone burden. Stone burden is measured as stone volume in mm^3 or stone density in Agatston units and is defined as new stone formation plus existing stone growth minus stone dissolution minus stone passage minus stone removal. In this study we assessed the effect of Cystone®, a common stone prevention treatment outside of Europe and the United States, on both improving urinary chemistries that determine solubility of cystine, and quantitatively assessed stone burden by CT scanning.

The current results did not document any beneficial effect of Cystone® on the urinary composition. However, the failure to find statistically significant change in urinary composition does not rule out a beneficial effect. Cystine capacity (supersaturation) in urine is not tightly correlated with urine chemistries. Cystone®, could induce urinary changes we did not measure that would increase urinary capacity for cystine.

Cystone® is purported to promote stone passage. However, despite multiple stone passages and surgeries to remove stones during this study, stone burden did not decrease. It is important to note that stone formers in this study tended to be those who had failed standard therapy, making this refractory population particularly difficult to treat. It is also possible an effect may have been apparent with longer follow-up. Importantly, no patient reported any side effects from Cystone® in accord with previously published studies. Therefore, we do not feel that use of this compound engenders undue risk. However, we cannot provide any evidence of efficacy.

Conclusion

This short-term study does not suggest that Cystone® affects those urinary chemistries commonly measured and known to influence cystine stone formation, nor does it decrease renal stone burden over a 1-year period. It is possible elements of the urine were affected that are not typically measured. A longer term study with more patients would be necessary to have power to definitively detect changes in stone events or enhanced stone passage, or effects on other stone types. Urine capacity for cystine should be measured. In any new study of Cystone®, the botanical authenticity of each individual herb will also need to be documented by the manufacturer using high-pressure liquid chromatography. Nevertheless, this short-term trial failed to find evidence that Cystone® decreases kidney stone burden in recurrent cystine stone formers, which might dampen enthusiasm for further study.

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