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D-Penicillamine; A Valuable and Tolerable Long-Term Rescue Therapy for Cystinuric Urolithiasis

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Abstract

Background: Cystinuric urolithiasis (CyU) is a rare autosomal recessive disorder due to defective proximal tubule reabsorption of cystine. It is associated with rapid and recurrent formation of large stones at an early age. Most patients are treated conservatively with adequate hydration (3 liters/day), alkalization of the urine with citrate to a pH between 7 - 8, and dietary modification to reduce salt and protein intake. Thiol, viz., D-penicillamine (DPA), is a drug that acts to form a complex with cystine that is 50 times more soluble than cystine itself, yet its use is limited by fear of its adverse effects and induction of membranous glomerulopathy. Patients and Methods: A total of 17 (1/3) of our CyU patients had failed such a conservative approach despite confirmed adequate compliance and had large and recurrent CyU. After their initial urological intervention (percutaneous nephrolithotomy or endoscopic laser lithotripsy), they received DPA 250 mg thrice daily. Results: Subsequent to DPA therapy, stone load (yearly urological intervention for large stones) decreased from 3 ± 1 to 0.4/year over a period of 93 ± 21 months ($p < 0.001$), with only 2 patients requiring minimal laser endoscopic lithotripsy. Moreover, their initial daily cystine output decreased from 1.9 ± 0.1 mmol to 0.55 ± 0.1 after 2 months of DPA therapy ($p < 0.001$) and remained low at the same level in all patients after 48 months and by the end of the study. Overall, the drug was well tolerated and none of the patients had significant proteinuria or blood dyskaryosis requiring drug discontinuation. Conclusion: Our data show that DPA can be an efficacious and safe long-term therapy for patients with high-load CyU.

Keywords

Cystinuria, D-Penicillamine, Membranous Glomerulopathy, Rescue Therapy, Stones, Urolithiasis

1. Introduction

Cystinuric urolithiasis (CyU) is mainly an autosomal recessive genetic disorder [1]. It results from mutations in the amino acid transporter gene, which is encoded by the heavy subunit (SLC3A1) and the light subunit (SLC7A9). This gene is responsible for the reabsorption of basic amino acids, viz. cystine, lysine, ornithine, and arginine, in the proximal convoluted tubules, leading to their high concentration in urine [2]. However, only high levels of cystine are pathological, with precipitations as CyU in neutral or acidic urine. CyU is a rare cause of urolithiasis (U) with a prevalence of 1%, yet a common one in children (8%). Eighty percent of CyU patients will have their first U during their first two decades, with an overall prevalence of 1/7000. However, it has a variable prevalence among different populations due to different consanguinity rates [3]. CyU is characterized by rapid and recurrent formation of large stones at an early age, which are difficult to 1) detect by ordinary x-ray and 2) fragment by conventional extracorporeal lithotripsy [4]. This disorder is associated with high morbidity, impairment of quality of life, and progressive renal loss due to obstructive uropathy if the diagnosis is missed or maltreated [5]. The currently recommended treatment strategy for CyU is based on a progressive approach, starting with the most conservative measures. Initial therapy involves 1) adequate hydration, 2) alkalization of the urine, and 3) dietary restriction of salt and protein intake. In refractory cases, treatment is extended to thiol-based medications [6]. D-penicillamine (DPA) is a thiol drug that acts to form a complex with cystine that is 50 times more soluble than cystine itself [7]. However, its use is hampered by fear of multiple adverse effects, viz. gastrointestinal, membranous glomerulopathy, and blood dyskaryosis. In this article, we present our retrospective analysis of our experience with its long-term safety and efficacy as a rescue therapy in CyU patients refractory to conservative approaches, in an attempt to limit the hesitancy in its use.

Surgical management of pediatric patients with cystine stones is similar to that in the adult population. However, cystine stones can be resistant to ESWL. Retrograde ureteroscopy with semirigid and flexible instruments is a good option for ureteral stones and also for renal stones less than 20 mm in diameter. The gold standard option for high-volume stones larger than 20 mm in diameter is percutaneous nephrolithotomy (PCNL).

2. Patients and Methods

Patients with refractory CyU were selected for DPA rescue therapy. In those patients, the diagnosis of CyU was established by: 1) positive nitroprusside urine

test, 2) typical urine hexagonal cystine crystals, 3) high daily urine cystine levels > 1.7 mmol (normal: <0.13 mmol), 4) positive cystine stone analysis by infrared spectroscopy. Refractory CyU disease was defined as recurrent high stone load that indicated > 2 urological interventions/year despite adequate conservative therapy [8]. High stone load was defined as stones >1 cm in diameter by CT scanning, particularly when they show growth despite medical therapy [6]. Adequate conservative therapy was defined as: 1) high daily water intake of 3 liters, 2) urine alkalinizer to pH between 7 - 8, and 3) dietary modification. Uralyt-U granules potassium-sodium-hydrogen-citrate with (2.5 g/1 measure) were used to keep urine pH between 7 and 8. Adequate urine alkalinization was confirmed daily by the patient before sleep by comparing the color of a test paper strip after soaking it with mid-stream fresh urine before receiving the last daily dose.

2.1. Exclusion Criteria

Patients with other types of urolithiasis diagnosed by laboratory and radiological tests, viz. renal tubular acidosis, primary hyperoxaluria, primary hyperparathyroidism, hypercalcemia (granulomatous and malignant diseases), primary hypercalciuria, as well as congenital urinary tract anomalies, especially medullary sponge kidneys and polycystic kidney disease.

2.2. Management

Initially, patients with a large stone load were stabilized after stone removal either by endoscopic laser lithotripsy or percutaneous nephrolithotomy (PCNL) if > 20 mm, as shown in **Figure 1** and **Figure 2**. Subsequently, they received a combination of 1) adequate conservative therapy, and 2) DPA at a dose of 250 mg thrice daily with vitamin B6 (Pyridoxine) at a dose of 50 mg daily.

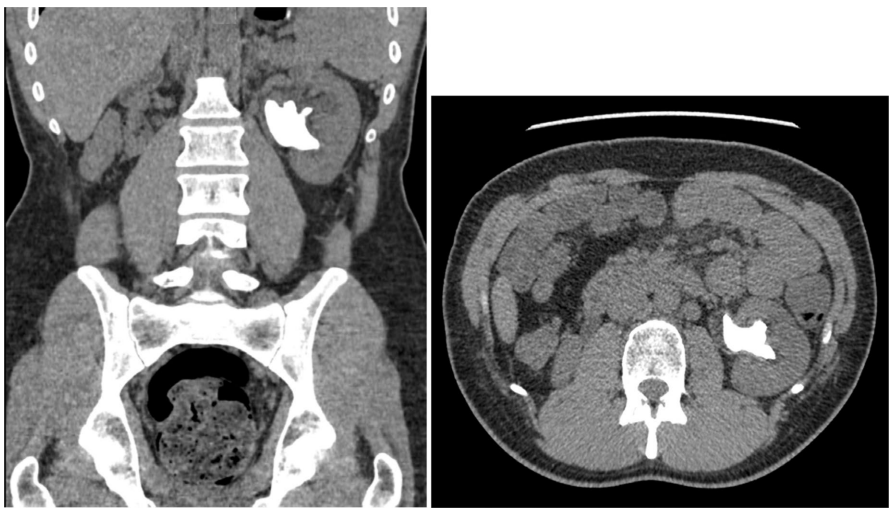

Figure 1. Initial presentation of a patient with a large staghorn calculus in the pelvis of the left kidney (hollow arrows) in the coronal and axial planes of the CT scan. The right kidney (solid arrows) is small after delayed and multiple interventions from previous cystinuric stones.

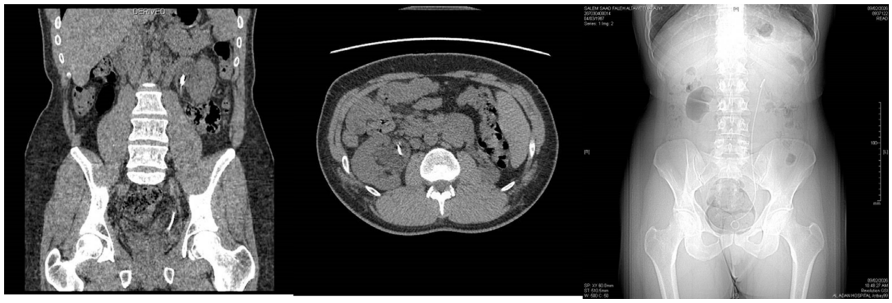

Figure 2. Post-operative coronal and axial CT images, as well as plain x-ray, showing complete removal of the staghorn calculus with double J stent (hollow arrow) in the pelvis of the left kidney.

2.3. Periodic Assessment

Patients were seen every month for the first 3 months, then every two months subsequently. At those visits, patients were assessed clinically, with laboratory testing and ultrasonography, as well as CT if indicated for new stone formation. Laboratory investigations included complete blood count, serum glucose, electrolytes, bicarbonate, renal and liver function tests, urine routine, and urinary pH. Serum bicarbonate and urinary pH were used to assess adequacy and compliance with urine alkalizer. Quantification of daily urine cystine output was done every month for the first 3 months, then every 6 months subsequently.

2.4. Primary Endpoint of the Study

Decrease in the number of procedures for stone removal served as the primary endpoint for assessment of the efficacy of DPA as a rescue therapy for the previously refractory CyU.

2.5. Statistical Analysis

SPSS statistical package version 25 was used for data entry and processing. The p-value < 0.05 was used as the cut-off level for significance. Since all variables were normally distributed, they were expressed as mean ± SD and compared using Student's t-test. Comparison of changes with time, following therapy, was done using t-test for repeated measures.

3. Results

In the past 15 years, we followed a total of 53 patients with confirmed CyU, of whom 17 had refractory disease despite adequate conservative therapy after 54 + 4 months of follow-up. The demographic data of the patients and their follow-up after DPA therapy are summarized in **Table 1**. These patients were young (17 + 3 years), of whom 6 (35%) were females. They had documented high stone load and had required 3 + 1 urological interventions for large stones per year. Subsequent to DPA therapy, stone load was minimal at 0.4 per year over a follow-up period of 93 + 21 months ($p < 0.001$), with most patients without stone recurrence (**Figure 3**). Only 2 patients had minimal laser endoscopic lithotripsy. Moreover, their initially high

daily cystine output (1.9 + 0.1 mmol) had decreased to 0.55 + 0.1 after 2 months of DPA therapy ($p < 0.001$) and remained low after 48 months of follow-up and by the end of the study. Overall, the drug was well tolerated, and none of the patients had significant gastrointestinal intolerance, proteinuria or blood dyskaryosis.

Table 1. Demographical data and follow-up of 17 patients with refractory cystinuric urolithiasis after D-penicillamine therapy.

Patients characteristics		
Gender (F/M)		6/11
Age (years)		17 ± 3
Duration of follow-up		
	Before D-penicillamine (months)	54 ± 4
	After D-penicillamine (months)	93 ± 21
Daily cystine urine output*		
	Before D-penicillamine (months)	1.9 ± 0.1
	After D-penicillamine (months)	
	2-months	0.55 ± 0.1
	48-months	0.54 ± 0.1
	By the end of the study	0.55 ± 0.1
Stone load/year**		
	Before D-penicillamine (months)	3 ± 1
	After D-penicillamine (months)	0.4 ± 0

N.B.: * & **; significant difference ($p < 0.001$) before and after.

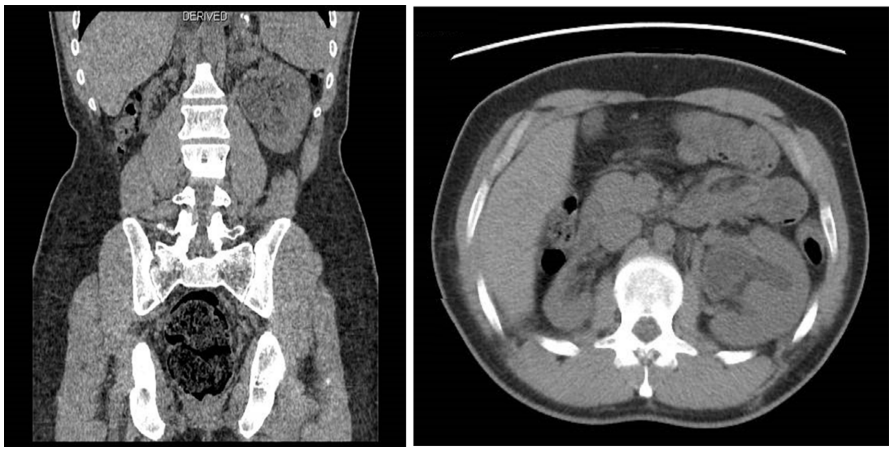

Figure 3. Coronal and axial CT images of the same patient with cystinuria, showing minimal post-operative hydronephrosis and absence of new urolithiasis after 48 months of d-penicillamine therapy.

4. Discussion

CyU is suspected in patients with: 1) early age of disease onset of U, 2) positive

family history of CyU, 3) recurrent and large U. Initially, other culprits of pediatric U should be excluded, viz. distal renal tubular acidosis and medullary sponge kidney. Subsequently, diagnosis of CyU can be established by: 1) positive screening with urine positive sodium cyanide-nitroprusside test and/or hexagonal urinary cystine crystals, 2) high urinary cystine levels, and 3) stone analysis. Genetic testing does not alter CyU management yet is indicated for family counseling. In the sodium cyanide-nitroprusside test, the cyanide converts cystine to cysteine, which then binds to the nitroprusside, creating an intense purple color in just a few minutes. The test typically turns positive at cystine levels > 37.5 umol/mmol creatinine [9]. Quantitative daily urinary cystine output is a confirmatory test that is positive if levels are higher than 39, 20, and 17 umol/mmol creatinine for patients < 1 month, 1 - 12 months, and >1 year, respectively. The normal daily urinary cystine excretion, in individuals > 1 year, is <0.13 mmol, while those with CyU excrete > 1.7 mmol/day [10]. The preferred method for stone chemical analysis is X-ray diffraction and infrared spectroscopy [11]. Overall, dietary management of CyU is aimed at lowering urinary stone load by hydration (up to 3 liters/daily), and low animal proteins (methionine) [12]. On the other hand, urine alkalinization is a key determinant of cystine solubility, and small changes in pH can have a big impact. At urinary pH of 7, the solubility of cystine is 1 mmol/L, which increases to 2 and 4 at pH 7.5 and 8.0, respectively [1]. Acetazolamide is a carbonic anhydrase inhibitor that increases urinary bicarbonate excretion and raises urinary pH levels. However, its efficacy is limited and is associated with poor tolerability, limited to hypocitraturia and metabolic acidosis [13]. In our study, nearly 1/3 of our CyU patients were refractory to conservative measures despite adequate and confirmed compliance, confirming the phenotypic heterogeneity of the disease [14]. Moreover, their daily urinary cystine output was > 1.9 umol. Hence, they qualified for treatment with thiol-based agents (TBA) as rescue therapy [6]. The sulfhydryl groups of TBA reduce the disulfide bond of the 2 cystine molecules, rendering them far more soluble than the original cystine molecule. The current list of TBA includes: Penicillamine, Captopril, Tiopronin, and Bucillamine. At the start of our study, only DPA was available and hence it was used. The improvement with DPA therapy was evident by the second month, with a decrease in urinary cystine output to 0.55 mmol, which persisted up to 48 months of follow-up (**Table 1**). Such improvement was associated with significant improvement in stone load, with a decrease of urological surgeries from 3/year to just 0.4/year, which were minor endoscopic ones. Pyridoxine (vitamin B6) was added to avoid its potential deficiency with long-term DPA therapy [15]. Previous reports described a large list of adverse effects with DPA therapy, with a prevalence up to 50%. The list included: fever, rash, loss of taste, arthritis, leukopenia, aplastic anemia, gastrointestinal disturbances, renal membranous nephropathy with proteinuria, immunosuppression, and pyridoxine (vitamin B6) deficiency [16]. Interestingly, these were not evident in our patient population and did not affect their drug compliance. Captopril is the first FDA-approved angiotensin-

converting enzyme inhibitor and has a sulfhydryl group that can form a bond with cysteine. It has been used off-label in cystinuria, yet the daily dose was 150 mg and it had limited efficacy and was associated with multiple side effects, viz. hyperkalemia, acute kidney injury, cough, and hypotension [17]. On the other hand, encouraging reports indicated that Tiopronin therapy was associated with better tolerability and fewer side effects than DPA [18]. Hence, it can be used as a valuable alternative for such a life-long disorder. Moreover, encouraging results on the use of a new dithiol compound (Bucillamine) in Asia are emerging [19]. Theoretically, the latter should be more effective than Tiopronin and better tolerated for its lower drug dosage. The limitations of the study are its limited sample size and being uncontrolled, yet the disease is rare and the patients' pre-treatment acted as a control group.

5. Conclusion

Vigilance in the diagnosis and management of CyU is indicated, as well as timely choice and selection of TPA agents, of which PAD remains a valuable drug.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Servais, A., Thomas, K., Dello Strologo, L., Sayer, J.A., Bekri, S., Bertholet-Thomas, A., *et al.* (2021) Cystinuria: Clinical Practice Recommendation. *Kidney International*, **99**, 48-58. https://doi.org/10.1016/j.kint.2020.06.035

[2] Sahota, A., Tischfield, J.A., Goldfarb, D.S., Ward, M.D. and Hu, L. (2019) Cystinuria: Genetic Aspects, Mouse Models, and a New Approach to Therapy. *Urolithiasis*, **47**, 57-66. https://doi.org/10.1007/s00240-018-1101-7

[3] Knoll, T., Zöllner, A., Wendt-Nordahl, G., Michel, M.S. and Alken, P. (2005) Cystinuria in Childhood and Adolescence: Recommendations for Diagnosis, Treatment, and Follow-up. *Pediatric Nephrology*, **20**, 19-24. https://doi.org/10.1007/s00467-004-1663-1

[4] Landau, E.H., Shenfeld, O.Z., Pode, D., Shapiro, A., Meretyk, S., Katz, G., *et al.* (2009) Extracorporeal Shock Wave Lithotripsy in Prepubertal Children: 22-Year Experience at a Single Institution with a Single Lithotriptor. *Journal of Urology*, **182**, 1835-1840. https://doi.org/10.1016/j.juro.2009.04.084

[5] Prot-Bertoye, C., Lebbah, S., Daudon, M., Tostivint, I., Bataille, P., Bridoux, F., *et al.* (2015) CKD and Its Risk Factors among Patients with Cystinuria. *Clinical Journal of the American Society of Nephrology*, **10**, 842-851. https://doi.org/10.2215/cjn.06680714

[6] Leslie, S.W., Sajjad, H. and Nazzal, L. (2023) Cystinuria. StatPearls.

[7] Andreassen, K.H., Pedersen, K.V., Osther, S.S., Jung, H.U., Lildal, S.K. and Osther,

P.J.S. (2016) How Should Patients with Cystine Stone Disease Be Evaluated and Treated in the Twenty-First Century? *Urolithiasis*, **44**, 65-76. https://doi.org/10.1007/s00240-015-0841-x

[8] Eisner, B.H., Goldfarb, D.S., Baum, M.A., Langman, C.B., Curhan, G.C., Preminger, G.M., *et al.* (2020) Evaluation and Medical Management of Patients with Cystine Nephrolithiasis: A Consensus Statement. *Journal of Endourology*, **34**, 1103-1110. https://doi.org/10.1089/end.2019.0703

[9] Nakagawa, Y. and Coe, F.L. (1999) A Modified Cyanide-Nitroprusside Method for Quantifying Urinary Cystine Concentration That Corrects for Creatinine Interference. *Clinica Chimica Acta*, **289**, 57-68. https://doi.org/10.1016/s0009-8981(99)00159-x

[10] Parvy, P.R., Bardet, J.I., Rabier, D.M. and Kamoun, P.P. (1988) Age-Related Reference Values for Free Amino Acids in First Morning Urine Specimens. *Clinical Chemistry*, **34**, 2092-2095. https://doi.org/10.1093/clinchem/34.10.2092

[11] Mohammadi, M., Shohani, A., Khorami, H., Nouri Mahdavi, K., IzadPanahi, M.H., Alizadeh, F., *et al.* (2018) The Effect of Selenium Supplementation on Cystine Crystal Volume in Patients with Cystinuria. *BioMedicine*, **8**, Article 26. https://doi.org/10.1051/bmdcn/2018080426

[12] Siener, R., Bitterlich, N., Birwé, H. and Hesse, A. (2021) The Impact of Diet on Urinary Risk Factors for Cystine Stone Formation. *Nutrients*, **13**, Article 528. https://doi.org/10.3390/nu13020528

[13] Sterrett, S.P., Penniston, K.L., Wolf, J.S. and Nakada, S.Y. (2008) Acetazolamide Is an Effective Adjunct for Urinary Alkalization in Patients with Uric Acid and Cystine Stone Formation Recalcitrant to Potassium Citrate. *Urology*, **72**, 278-281. https://doi.org/10.1016/j.urology.2008.04.003

[14] Alghamdi, M., Alhasan, K.A., Taha Elawad, A., Salim, S., Abdelhakim, M., Nashabat, M., *et al.* (2020) Diversity of Phenotype and Genetic Etiology of 23 Cystinuria Saudi Patients: A Retrospective Study. *Frontiers in Pediatrics*, **8**, Article 569389. https://doi.org/10.3389/fped.2020.569389

[15] Brown, M.J., Ameer, M.A., Daley, S.F. and Beier, K. (2023) Vitamin B6 Deficiency. StatPearls.

[16] Kumar, V., Singh, A.P., Wheeler, N., Galindo, C.L. and Kim, J. (2021) Safety Profile of D-Penicillamine: A Comprehensive Pharmacovigilance Analysis by FDA Adverse Event Reporting System. *Expert Opinion on Drug Safety*, **20**, 1443-1450. https://doi.org/10.1080/14740338.2021.1956460

[17] Eggermann, T., Venghaus, A. and Zerres, K. (2012) Cystinuria: An Inborn Cause of Urolithiasis. *Orphanet Journal of Rare Diseases*, **7**, Article No. 19. https://doi.org/10.1186/1750-1172-7-19

[18] Rezaee, M.E., Rule, A.D. and Pais, V.M. (2019) What Are the Main Challenges to the Pharmacological Management of Cystinuria? *Expert Opinion on Pharmacotherapy*, **21**, 131-133. https://doi.org/10.1080/14656566.2019.1691522

[19] Daga, S., Palit, V., Forster, J.A., Biyani, C.S., Joyce, A.D. and Dimitrova, A.B. (2021) An Update on Evaluation and Management in Cystinuria. *Urology*, **149**, 70-75. https://doi.org/10.1016/j.urology.2020.12.025