SUCCESSFUL TREATMENT OF HOMOZYGOUS CYSTINURIA WITH CAPTOPRIL

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Objective: Cystinuria is an autosomal recessive hereditary disorder associated with nephrolithiasis and its attendant complications. Traditional management using oral alkali, D-penicillamine, or mercaptopropionyglycine in an attempt to increase urinary cystine solubility is often unsuccessful due to intolerable side-effects. The aim of this study was to determine, if captopril could reduce urinary cystine excretion in homozygous cystinuric patients.

Patients and Methods: Three cystinuric patients with a history of multiple cystine stones despite previous traditional therapy were treated with 150 mg captopril daily for 3 years after determination of their baseline 24-hour urine cystine excretion. Cystine excretion studies were repeated subsequently at 6-month intervals.

Results: The baseline 24-hour urine cystine excretion was within the expected limits for homozygous cystinuria in all patients (1072, 862 and 959 mg cystine per gm creatinine per 24 hours). After institution of captopril treatment, all patients had a significant decrease in urinary cystine levels (374, 313 and 451 mg cystine per gm creatinine per 24 hours). No patient experienced recurrent nephrolithiasis or adverse drug effects.

Conclusion: We conclude that captopril can significantly decrease urinary cystine excretion in patients with homozygous cystinuria. Captopril should be considered an alternative to traditional drug management of cystinuria.

Key Words: lithiasis, captopril, urinary calculi, cystinuria.

INTRODUCTION

Cystinuria is a complex hereditary disorder transmitted as an autosomal recessive trait[1,2]. Its basis is a defect in the transport of cystine and other dibasic amino-acids by epithelial cells of the renal tubule and small intestine[3]. The renal defect results in excretion of excessive amounts of unreabsorbed cystine in the urine and resultant stone formation, accounting for approximately 1% of all renal stones. Those afflicted present with renal colic and subsequent urinary tract obstruction, recurrent infection, and renal insufficiency[3]

The diagnosis is suggested by cystine crystalluria in the setting of nephrolithiasis and is confirmed by analysis of the stone and demonstration of increased cystine excretion.

Traditional management of cystinuria is directed at decreasing the urinary concentration of cystine while increasing its urinary solubility[4]. Thus, treatment comprises maintaining a large urine volume following a low methionine diet, and urine alkalinisation using oral alkali and acetazolamide. If this proves unsuccessful, then medication that promotes cystine solubility via formation of a thiol-cysteine disulfide, such as acetylcysteine, D-penicillamine[5], and mercaptopropionylglycine (MPG)[6] can be used. D-penicillamine is the most successful of these medications, acting to form a

penicillamine-cysteine disulfide compound that is 50 times more soluble than cystine[3]. However, these therapeutic modalities often are ineffective due to the patient's inability to comply with dietary manipulation, massive oral fluid intake, alkali intolerance, and adverse side-effects of the medication.

Captopril is an angiotensin-converting enzyme inhibitor that contains a sulfhydryl group similar to D-penicillamine. It can potentially form a disulfide bond with cysteine, which may be useful in the therapy of cystinuria[7,8].

The present study was carried out to determine the efficacy of captopril on urinary cystine excretion and on the formation or growth of calculi in homozygous cystinuria.

PATIENTS AND METHODS

Three patients (aged 15, 44 and 26 years) with homozygous cystinuria and documented recurrent cystine stone formation were studied. Before the institution of captopril treatment all 3 patients were receiving standard therapy for cystine stones, including forced hydration, a low methionine diet and urinary alkalization with sodium bicarbonate or potassium citrate at a dose titrated to keep urine pH greater than 7.5. D-penicillamine was refused as a therapeutic modality by the patients due to intolerable side-effects. In our study, failure of standard therapy was defined by the formation of new stones, stone growth, significant side-effects precluding continuation of the treatment or failure to decrease urinary cystine excretion. Despite appropriate medical management, our 3 patients had undergone a total of 10 interventional procedures for stone removal (2, 5 and 3, respectively) including open lithotomy (2), percutaneous nephrolithotomy (3), ureteroscopy (1) and extracorporeal shock wave lithotripsy (4).

A daily fluid intake of 2.0 to 2.5 L was maintained in each patient. Captopril treatment was started with an initial dose of 75 mg daily divided into 3 doses. This dose

was increased after 2 weeks to 150 mg daily, also in 3 divided doses. The blood pressure was recorded before treatment and at regular follow-up visits. The 24-hour urinary cystine and creatinine values were recorded for all patients at 6-month intervals. All patients were normotensive and had normal renal function at the start of captopril therapy. The urinary cystine levels were assayed by elution chromatography on ion-exchange resin columns with an automated amino-acid analyser. Serial radiographic studies were obtained during treatment to help monitor stone activity. These studies included plain radiographs of the abdomen in all patients and ultrasonography or excretory urography as necessary. The patients were followed for 3 years.

RESULTS

The patients experienced no adverse effects attributable to captopril, specifically no orthostatic hypotension, dizziness, azotemia, proteinuria, or leukopenia.

Baseline 24-hour urine cystine excretion was within the expected limits for homozygous cystinuria in all patients (1072, 862 and 959 mg cystine per gm creatinine per 24 hours). After institution of captopril, all patients had a significant decrease in urinary cystine levels. The 24-hour urinary cystine levels on captopril were 374, 313 and 451 mg cystine per gm creatinine per 24 hours (Table 1). No patient experienced recurrent cystine crystalluria, symptomatic nephrolithiasis, or new renal stone formation.

DISCUSSION

Cystine, the least soluble of the dibasic amino-acids, is the disulfide form of cysteine[3]. The solubility of cystine at a urine pH between 4.5 and 7.0 is approximately 200 to 300 mg/L. In non-cystinuric patients, urinary cystine excretion is approximately 30 mg/24 hours[1]. However, in a homozygous cystinuric patient, excretion commonly exceeds 400 mg/L, which in turn leads to cystine precipitation and subsequent formation of renal calculi.

Table 1: Effect of Captopril over a 3-Year-Period on 24-Hour Urinary Cystine Excretion Measured at Baseline and at Subsequent 6-Month Intervals.

Case no.	Baseline urinary cystine excretion*	Urinary cystine excretion on captopril*						% Reduction from baseline
		6 months	12 months	18 months	24 months	30 months	36 months	
1	1072	954	833	683	576	410	374	66
2	862	750	687	602	451	396	313	64
3	959	816	732	693	607	510	451	53

*Expressed as mg cystine per gm creatinine per 24 hours.

The ability to enhance cystine solubility depends on the formation of a thiol-cysteine mixed disulfide. Both D-penicillamine and MPG enhance solubility via formation of penicillamine-cysteine and MPG-cysteine disulfide compounds[1]. Although D-penicillamine adequately reduces stone formation, its use has been limited by the 30% to 50% incidence of intolerable and at times serious side-effects[5,6]. Despite the moderately improved effectiveness of MPG compared with D-penicillamine, there are numerous side-effects associated with MPG, including gastric intolerance, skin rash, fever, proteinuria, and nephrotic syndrome[6].

Captopril also exerts its solubilizing effect via formation of a disulfide compound (Fig. 1) and is a more attractive agent compared with D-penicillamine and MPG for two reasons. First, the captopril-cysteine disulfide is 200 times more soluble than cystine (four times more soluble than the D-penicillamine and MPG-disulfide compounds)[7,9] and second, captopril has relatively few side-effects when used at the doses we are currently administering. In fact, the incidence of serious side-effects associated with captopril, including orthostatic hypotension, dizziness, azotemia, proteinuria, or leukopenia, has been reported to be very low. Groel et al. studied 7103 hypertensive patients receiving captopril for up to 4 years and found side-effects in 11% of patients[10]. In a study on the use of captopril in non-hypertensive patients, Martin et al. also found a low incidence of side-effects[11]. Only 13% of their patients treated with captopril at up to 150 mg daily for severe rheumatoid arthritis suffered side-effects requiring discontinuation of the drug.

As in our patients, captopril has been previously used to treat patients with cystinuria. Sloand and Izzo first used captopril successfully in the therapy of cystinuria when they treated two hypertensive siblings who were both homozygous cystinurics[7]. In contrast to these 2 patients, our patients were normotensive and, therefore, they did not require captopril for its antihypertensive effect. Sloand and Izzo documented a significant decrease in urinary cystine excretion in both patients as manifested by a 70% and 93% reduction with titration to 150 mg/day and 75 mg/day of captopril, respectively. Since the publication of this study, there have been conflicting reports regarding the efficacy of captopril in decreasing urinary cystine[2,3,8,9].

Our three patients, who received daily doses of 150 mg/day of captopril, have maintained a reduction in urinary cystine of 66%, 64% and 53%, respectively. At this level of urinary cystine, there has been no recurrence of stones and none of the patients, not even our 15-year-old patient (body weight 62.5 kg), has experienced any adverse effects attributable to captopril. This is similar to the findings of Michelakakis et al. who reported that a 9-year-old boy diagnosed as cystinuric and treated by captopril administered at 2.5 mg/kg per day for 34 months did not develop any signs of captopril side-effects during treatment[12]. In our study, captopril proved to be effective also in the child, and in all three patients, arterial blood pressure, as well as
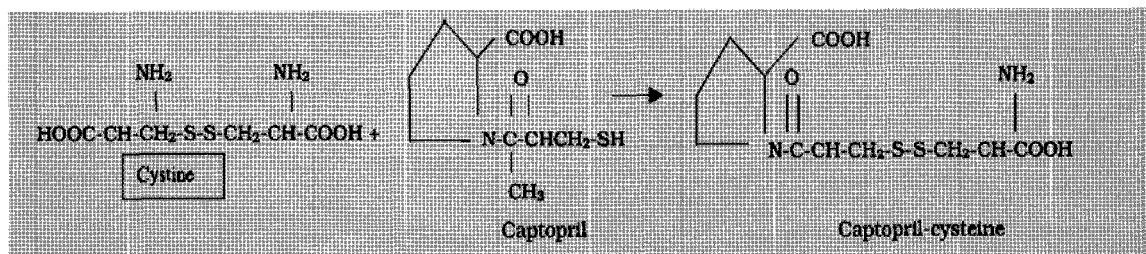
Fig. 1: Captopril combines with half-cystine to form a more soluble mixed disulfide with cysteine.

all laboratory parameters concerning renal function, were within normal limits at follow-up.

Long-term studies on a larger number of patients with cystinuria will need to be conducted to substantiate our findings. During the follow-up, intermittent treatment or a reduced dose of captopril may be tried, if urinary cystine excretion is below 250 mg cystine per gm creatinine daily.

In conclusion, traditional management often is either marginally effective or poorly tolerated by the patient. If hydration and alkalinisation fail to prevent cystine stone recurrence the next step in the treatment algorithm for cystinuria should be the introduction of captopril to decrease the urinary cystine excretion. Captopril, due to its ability to form the solubilizing thiol-cysteine disulfide and its relatively low side-effect profile, appears to be successful in the treatment of cystinuria. Although long-term follow-up is required to evaluate this form of therapy, captopril should be considered a useful adjuvant, if not primary therapy for cystinuria.

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RESUME

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