

Case study: importance of early management of cystinuria

An adult male patient experienced multiple cystine stones and had several urologic procedures at an early age. Starting treatment with THIOLA® (tiopronin) tablets and conservative management led to a reduction in cystine stones and no hospitalizations for more than 10 years.^{1,a}

Key clinical details of patient LS' cystine stone case¹

- Utilization of 24-hour urine cystine testing led to diagnosis of cystinuria
- Patient underwent several cystine stone events and urologic procedures
- Had severely reduced kidney function resulting from local obstruction of multiple renal calyces and several urologic procedures
- Patient prescribed THIOLA and conservative management, including a low-sodium and low-protein diet, and alkali treatment
- No hospital admissions for 10 years and reduced cystine stone burden following treatment with THIOLA and conservative management
 - Regimen includes low-sodium and low-protein diet, and potassium citrate for urine alkalinization
 - Current estimated glomerular filtration rate (GFR) is excellent with a serum creatinine concentration of 1.0 mg/dL

^aIndividual patient response. Not all patients will respond similarly to the same medical treatment.

Indications: THIOLA® (tiopronin) tablets are indicated for the prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria with urinary cystine >500 mg/day, who are resistant to treatment with conservative measures of high fluid intake, alkali and diet modification, or who have adverse reactions to d-penicillamine.

Important Safety Information

Contraindications: THIOLA is contraindicated during pregnancy (except where the benefits clearly outweigh the risks), in nursing mothers, and in patients who have previously developed agranulocytosis, aplastic anemia or thrombocytopenia while on this medication.

Please see additional Important Safety Information on the following pages and accompanying full Prescribing Information.

Reference: 1. Goldfarb DS, Grasso M. Case studies in cystinuria. *Urol Nurs.* 2017;37(2):90-93. doi:10.7257/1053-816X.2017.37.2.90.


Thiola[®]
(tiopronin) tablets
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Diagnosis and treatment plan¹

AGE 13 Patient presented with multiple large stones mistaken for “calcifications”; 24-hour urine cystine test was utilized to confirm a diagnosis of cystinuria

AGE 14 Patient underwent many urologic procedures to remove staghorn stones

- Upon removal of cystine stones, patient was instructed to increase fluid intake, limit dietary protein and sodium, and initiate alkali treatment
- Patient was prescribed THIOLA® (tiopronin) tablets, 600 mg, twice per day

Effect on renal function¹

AGES 20-22 Kidney function compromised from multiple urologic procedures

- 4 episodes of renal colic with increasing serum creatinine caused by obstructive uropathy; ureteral stents placed in each instance
- Kidney function was severely reduced on the right side; left kidney was larger than the right and was responsible for 91% of his total GFR
- Ileal ureter constructed

Long-term management¹

AGE 22+ Patient has been on THIOLA and conservative management for 10 years with no hospital admissions and a reduction in cystine stone burden

Key takeaways and treatment plan¹

In the management of cystinuria, it is important to act promptly to

- Identify cystinuria and initiate appropriate medical treatment, which may help reduce cystine stone production and avoid more severe disease sequelae
- Assess the potential impact of recurrent obstructive cystine stones on renal function so that potential end-stage renal disease can be delayed or prevented

You can help patients achieve the goal of stone-free and prevent the next surgery by optimizing their treatment plans early on

The American Urological Association recommends using cystine-binding thiol drugs, such as THIOLA, as the next line of therapy when therapeutic lifestyle changes fail to prevent stones from forming.¹

Monitor cystine levels with a 24-hour urine cystine test to assess the proper dosing needed to keep cystine levels below the line of solubility (generally <250 mg/L).^{2,3}

Adjust THIOLA dosage based on urinary cystine concentration.³

THE RECOMMENDED STARTING DOSAGE OF THIOLA IS 800 MG/DAY IN ADULTS³:

- 15 mg/kg/day in children ≥9 years of age³
- Taken in 3 divided doses, 1 hour before or 2 hours after a meal, as food can affect how THIOLA is absorbed in the body, potentially lessening the effect of THIOLA³

In conjunction with a conservative management plan, optimizing THIOLA dosing is the best way to help patients with cystinuria potentially become stone-free by keeping cystine levels below the line of solubility (generally <250 mg/L).^{3,4}

Optimizing THIOLA dosing can help patients achieve significant reduction in stone burden⁵

In a multicenter trial that evaluated treatment with THIOLA in 66 patients with cystinuria, 14 treatment-naïve patients who received a mean THIOLA dosage of 1193 ± 450 mg/day for 4 months to 4 years (mean, 1.59 years) achieved

- Stone remission rate of 71.4% (cessation of stone formation)
- Stone reduction rate of 94.1% (reduced rate of new stone formation)

Important Safety Information (cont'd)

Warnings and Precautions:

- While no deaths have been reported with THIOLA treatment, THIOLA can potentially cause all the serious adverse reactions reported for d-penicillamine, including death.
- Hematologic abnormalities requiring drug discontinuation may occur: inform patients to report promptly signs or symptoms of hematologic abnormalities.
- Proteinuria, sometimes severe enough to cause nephrotic syndrome: monitor affected patients closely.

Please see additional Important Safety Information on back cover and accompanying full Prescribing Information.

References: **1.** Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. *J Urol.* 2014;192(2):316–324. doi:10.1016/j.juro.2014.05.006. **2.** Knoll T, Zöllner A, Wendt-Nordahl G, Michel MS, Alken P. Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment, and follow-up. *Pediatr Nephrol.* 2005;20(1):19–24. doi:10.1007/s00467-004-1663-1. **3.** THIOLA [package insert]. San Antonio, TX: Mission Pharmacal Company; 2017. **4.** Pareek G, Steele TH, Nakada SY. Urological intervention in patients with cystinuria is decreased with medical compliance. *J Urol.* 2005;174(6):2250–2252. doi:10.1097/01.ju.00000181817.89703.66. **5.** Pak CYC, Fuller C, Sakhaee K, et al. Management of cystine nephrolithiasis with alpha-mercaptopyropionylglycine. *J Urol.* 1986;136(5):1003–1008.

Thiola[®]
(tiopronin) tablets
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Indications: THIOLA® (tiopronin) tablets are indicated for the prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria with urinary cystine >500 mg/day, who are resistant to treatment with conservative measures of high fluid intake, alkali and diet modification, or who have adverse reactions to d-penicillamine.

Important Safety Information

Contraindications: THIOLA is contraindicated during pregnancy (except where the benefits clearly outweigh the risks), in nursing mothers, and in patients who have previously developed agranulocytosis, aplastic anemia or thrombocytopenia while on this medication.

Warnings and Precautions:

- While no deaths have been reported with THIOLA treatment, THIOLA can potentially cause all the serious adverse reactions reported for d-penicillamine, including death.
- Hematologic abnormalities requiring drug discontinuation may occur: inform patients to report promptly signs or symptoms of hematologic abnormalities.
- Proteinuria, sometimes severe enough to cause nephrotic syndrome: monitor affected patients closely.
- Discontinue THIOLA therapy if there are findings suggestive of Goodpasture's syndrome, myasthenic syndrome, or myasthenia gravis. If pemphigus-type reactions occur, discontinue therapy and consider steroid treatment.
- Inform patients about potential complications; advise them to promptly report any treatment-emergent signs or symptoms.
- To reduce the risk of serious complications, the following tests should be conducted:
 - Peripheral blood counts, direct platelet counts, hemoglobin, serum albumin, liver function tests, 24-hour urinary protein, routine urinalysis: 3-6 month intervals
 - Urinary cystine analysis: frequently during dose optimization, and at 6 month intervals thereafter
 - Abdominal roentgenogram: annually
- In animal studies, THIOLA has been shown to cause fetal harm. THIOLA should only be used during pregnancy if the potential benefit justifies potential risk to the fetus.
- THIOLA should not be used in nursing mothers.
- The safety and efficacy of THIOLA in children under 9 years of age have not been established.

Adverse Reactions:

Adverse reactions associated with THIOLA include the following:

- Drug fever during the first month
- Generalized rash with pruritus
- Lupus erythematosus-like drug reaction (e.g., fever, arthralgia, lymphadenopathy, positive antinuclear antibody test)
- Hypogeusia
- Vitamin B₆ deficiency (uncommon)
- Wrinkling and friability of skin
- Jaundice and abnormal liver function tests (in non-cystinuric conditions)

THIOLA is associated with fewer or less severe reactions than d-penicillamine, however the following adverse reactions may occur:

- *Gastrointestinal* (nausea, emesis, diarrhea, anorexia, abdominal pain, bloating, flatus)
- *Impairment in taste or smell*
- *Dermatologic* (pharyngitis, oral ulcers, rash, ecchymosis, pruritus, urticaria, warts, skin wrinkling, pemphigus, elastosis perforans serpiginosa)
- *Hypersensitivity reactions* (laryngeal edema, dyspnea, respiratory distress, fever, chills, arthralgia, weakness, fatigue, myalgia, adenopathy)
- *Hematologic* (increased bleeding, anemia, leukopenia, thrombocytopenia, eosinophilia)
- *Renal* (proteinuria, nephrotic syndrome, hematuria)
- *Pulmonary* (bronchiolitis, hemoptysis, pulmonary infiltrates, dyspnea)
- *Neurologic* (myasthenic syndrome)

These reactions are more likely to occur during THIOLA therapy for patients who had previously shown toxicity to d-penicillamine.

Please see accompanying full Prescribing Information.

Retrophin®

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Thiola®
(tiopronin) tablets
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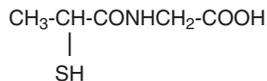
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THIOLA®

(Tiopronin) Tablets

FULL PRESCRIBING INFORMATION

DESCRIPTION: THIOLA® (Tiopronin) is a reducing and complexing thiol compound. Tiopronin is N-(2-Mercaptopropionyl) glycine and has the following structure:



Tiopronin has the empirical formula $\text{C}_5\text{H}_9\text{NO}_3\text{S}$ and a molecular weight of 163.20. In this drug product tiopronin exists as a dl racemic mixture.

Tiopronin is a white crystalline powder which is freely soluble in water.

THIOLA® tablets are white, sugar coated tablets, each containing 100 mg. of Tiopronin and are taken orally.

Inactive ingredients: Calcium carbonate, carnauba wax, ethyl cellulose, Eudragit E 100, hydroxypropyl cellulose, lactose, magnesium stearate, povidone, sugar, talc, titanium dioxide.

CLINICAL PHARMACOLOGY: THIOLA® is an active reducing agent which undergoes thiol-disulfide exchange with cystine to form a mixed disulfide of Thiola-cystine.



Thiola Cystine \rightleftharpoons Thiola-cystine

From this reaction a water-soluble mixed disulfide is formed and the amount of sparingly soluble cystine is reduced. When THIOLA® is given orally, up to 48% of dose appears in urine during the first 4 hours and up to 78% by 72 hours. Thus, in patients with cystinuria, sufficient amount of THIOLA® or its active metabolites could appear in urine to react with cystine, lowering cystine excretion.

The decrement in urinary cystine produced by THIOLA® is generally proportional to the dose. A reduction in urinary cystine of 250-350 mg/day at a THIOLA® dosage of 1 g/day, and a decline of approximately 500 mg/day at a dosage of 2 g/day, might be expected. THIOLA® causes a sustained reduction in cystine excretion without apparent loss of effectiveness. THIOLA® has a rapid onset and offset of action, showing a fall in cystine excretion on the first day of administration and a rise on the first day of drug withdrawal.

INDICATIONS AND USAGE: THIOLA® is indicated for the prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria with urinary cystine greater than 500 mg/day, who are resistant to treatment with conservative measures of high fluid intake, alkali and diet modification, or who have adverse reactions to d-penicillamine.

Cystine stones typically occur in approximately 10,000 persons in the United States who are homozygous for cystinuria. These persons excrete abnormal amounts of cystine in urine of over 250 mg/g creatinine, as well as excessive amounts of other dibasic amino acids (lysine, arginine and ornithine). In addition, they show varying intestinal transport defects for these same amino acids. The stone formation is the result of poor aqueous solubility of cystine.

Since there are no known inhibitors of the crystallization of cystine, the stone formation is determined primarily by the urinary supersaturation of cystine. Thus, cystine stones could theoretically form whenever urinary cystine concentration exceeds the solubility limit. Cystine solubility in urine is pH-dependent, and ranges from 170-300 mg/liter at pH 5, 190-400 mg/liter at pH 7 and 220-500 mg/liter at pH 7.5.

The goal of therapy is to reduce urinary cystine concentration below its solubility limit. It may be accomplished by dietary means aimed at reducing cystine synthesis and by a high fluid intake in order to increase urine volume and thereby lower cystine concentration.

Unfortunately, the above conservative measures alone may be ineffective in controlling cystine stone formation in some homozygous patients with severe cystinuria (urinary cystine exceeding 500 mg/day). In such patients, d-penicillamine has been used as an additional therapy. Like THIOLA®,

d-penicillamine undergoes thiol-disulfide exchange with cystine, thereby lowering the amount of sparingly soluble cystine in urine.

However, d-penicillamine treatment is frequently accompanied by adverse reactions, such as dermatologic complications, hypersensitivity reactions, hematologic abnormalities and renal disturbances. THIOLA® may have a particular therapeutic role in such patients.

CONTRAINDICATIONS: The use of THIOLA® during pregnancy is contraindicated, except in those with severe cystinuria where the anticipated benefit of inhibited stone formation clearly outweighs possible hazards of treatment (see PRECAUTIONS).

THIOLA® should not be begun again in patients with a prior history of developing agranulocytosis, aplastic anemia or thrombocytopenia on this medication.

Mothers maintained on THIOLA® treatment should not nurse their infants.

WARNINGS: Despite apparent lower toxicity of THIOLA®, THIOLA® may potentially cause all the serious adverse reactions reported for d-penicillamine. Thus, although no death has been reported to result directly from THIOLA® treatment, a fatal outcome from THIOLA® is possible, as has been reported with d-penicillamine therapy from such complications as aplastic anemia, agranulocytosis, thrombocytopenia, Goodpasture's syndrome or myasthenia gravis.

Leukopenia of the granulocytic series may develop without eosinophilia. Thrombocytopenia may be immunologic in origin or occur on an idiosyncratic basis. The reduction in peripheral blood white count to less than 3500/cubic mm or in platelet count to below 100,000 cubic mm mandates cessation of therapy. Patients should be instructed to report promptly the occurrence of any symptom or sign of these hematological abnormalities, such as fever, sore throat, chills, bleeding or easy bruisability.

Proteinuria, sometimes sufficiently severe to cause nephrotic syndrome, may develop from membranous glomerulopathy. A close observation of affected patients is mandatory.

The following complications, though rare, have been reported during d-penicillamine therapy and could occur during THIOLA® treatment. When there are abnormal urinary findings associated with hemoptysis and pulmonary infiltrates suggestive of Goodpasture's syndrome, THIOLA® treatment should be stopped. Appearance of myasthenic syndrome or myasthenia gravis requires cessation of treatment. When pemphigus-type reactions develop, THIOLA® therapy should be stopped. Steroid treatment may be necessary.

PRECAUTIONS: Patients should be advised of the potential development of complications and to report promptly the occurrence of any symptom or sign of them.

To help monitor potential complications, the following tests are recommended: peripheral blood counts, direct platelet count, hemoglobin, serum albumin, liver function tests, 24-hour urinary protein and routine urinalysis at 3-6 month intervals during treatment. In order to assess effect on stone disease, urinary cystine analysis should be monitored frequently during the first 6 months when the optimum dose schedule is being determined, and at 6-month intervals thereafter. Abdominal roentgenogram (KUB) is advised on a yearly basis to monitor the size and appearance/disappearance of stone(s).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term carcinogenicity studies in animals have not been performed. High doses of THIOLA® in experimental animals have been shown to interfere with maintenance of pregnancy and viability of the fetus.

USE IN PREGNANCY: Pregnancy category C. D-penicillamine has been shown to cause skeletal defects and cleft palates in the fetus when given to pregnant rats at 10 times the dose recommended for human use. A similar teratogenicity might be expected for THIOLA® although no such findings could be related to the drug in studies in mice and rats at doses up to 10 times the highest recommended human dose.

There are no adequate and well-controlled studies in pregnant women. THIOLA® should be used during pregnancy only if the potential benefit justifies potential risk to the fetus.

NURSING MOTHERS: Because THIOLA® may be excreted in milk and because of the potential serious adverse reactions of nursing infants from THIOLA®, mothers taking THIOLA® should not nurse their infants.

PEDIATRIC USE: Safety and effectiveness below the age of 9 have not been established.

ADVERSE REACTIONS: Some patients may develop drug fever, usually during the first month of therapy. THIOLA® treatment should be discontinued until the fever subsides. It may be reinstated at a small dose, with a gradual increase in dosage until the desired level is achieved.

A generalized rash (erythematous, maculopapular or morbilliform) accompanied by pruritis may develop during the first few months of treatment. It may be controlled by antihistamine therapy, typically recedes when THIOLA® treatment is discontinued, and seldom recurs when THIOLA® treatment is restarted at a lower dosage. Less commonly, rash may appear late in the course of treatment (of more than 6 months). Located usually in the trunk, the late rash is associated with intense pruritis, recedes slowly after discontinuing treatment, and usually recurs upon resumption of treatment.

A drug reaction simulating lupus erythematosus, manifested by fever, arthralgia and lymphadenopathy may develop. It may be associated with a positive antinuclear antibody test, but not necessarily with nephropathy. It may require discontinuance of THIOLA® treatment.

A reduction in taste perception may develop. It is believed to be the result of chelation of trace metals by THIOLA®. Hypogeusia is often self-limiting.

Unlike during d-penicillamine therapy, vitamin B₆ deficiency is uncommonly associated with THIOLA® treatment.

Some patients may complain of wrinkling and friability of skin. This complication usually occurs after long-term treatment, and is believed to result from the effect of THIOLA® on collagen.

A multiclinic trial involving 66 cystinuric patients in the United States indicated that THIOLA® is associated with fewer or less severe adverse reactions than d-penicillamine. Among those who had to stop taking d-penicillamine due to toxicity, 64.7% could take THIOLA®. In those without prior history of d-penicillamine treatment, only 5.9% developed reactions of sufficient severity to require THIOLA® withdrawal. A review of available literature supports the findings from this trial.

Despite this apparent reduced toxicity to THIOLA® relative to d-penicillamine, THIOLA® treatment may potentially be associated with all the adverse reactions reported with d-penicillamine. They include:

Gastrointestinal side-effects (nausea, emesis, diarrhea or soft stools, anorexia, abdominal pain, bloating or flatus) in about 1 in 6 patients;

Impairment in taste and smell in about 1 in 25 patients;

Dermatologic complications (pharyngitis, oral ulcers, rash, ecchymosis, pruritis, urticaria, warts, skin wrinkling, pemphigus, elastosis perforans seriginosa) in about 1 in 6 patients;

Hypersensitivity reactions (laryngeal edema, dyspnea, respiratory distress, fever, chills, arthralgia, weakness, fatigue, myalgia, adenopathy) in about 1 in 25 patients;

Hematologic abnormalities (increased bleeding, anemia, leukopenia, thrombocytopenia, eosinophilia) in about 1 in 25 patients;

Renal complications (proteinuria, nephrotic syndrome, hematuria) in about 1 in 20 patients;

Pulmonary manifestations (bronchiolitis, hemoptysis, pulmonary infiltrates, dyspnea) in about 1 in 50 patients;

Neurologic complications (myasthenic syndrome) in about 1 in 50 patients.

These reactions are more likely to develop during THIOLA® therapy among patients who had previously shown toxicity to d-penicillamine.

In patients who had previously manifested adverse reactions to d-penicillamine, adverse reactions to THIOLA® are more likely to occur than in patients who took THIOLA® for the first time. A close supervision with a careful monitoring of potential side effects is mandatory during THIOLA® treatment. Patients should be told to report promptly any symptoms suggesting toxicity. The treatment with THIOLA® should be stopped if severe toxicity develops.

Jaundice and abnormal liver function tests have been reported during THIOLA® therapy for non-cystinuric conditions. A direct cause and effect relationship, based upon these foreign reports, has not been established. Although such complications were not encountered in the small multi-center trials in the United States, patients should be carefully monitored and if any abnormalities are noted, the drug should be discontinued and the patient treated by appropriate measures.

DOSAGE AND ADMINISTRATION: It is recommended that a conservative treatment program should be attempted first. At least 3 liters of fluid (10-10 oz. glassfuls) should be provided, including two glasses with each meal and at bedtime. The patients should be expected to awake at night to urinate; they should drink two more glasses of fluids before returning to bed. Additional fluids should be consumed if there is excessive sweating or intestinal fluid loss. A minimum urine output of 2 liters/day on a consistent basis should be sought. A modest amount of alkali should be provided in order to maintain urinary pH at a high normal range (6.5-7.0). Potassium alkali are advantageous over sodium alkali, because they do not cause hypercalciuria and are less likely to cause the complication of calcium stones.

Excessive alkali therapy is not advisable. When urinary pH increases above 7.0 with alkali therapy, the complication of calcium phosphate nephrolithiasis may ensue because of the enhanced urinary supersaturation of hydroxyapatite in an alkaline environment.

In patients who continue to form cystine stones on the above conservative program, THIOLA® may be added to the treatment program. THIOLA® may also be substituted for d-penicillamine in patients who have developed toxicity to the latter drug. In both situations, the conservative treatment program should be continued.

The dose of THIOLA® should not be arbitrary but should be based on that amount required to reduce urinary cystine concentration to below its solubility limit (generally <250 mg/liter). The extent of the decline in cystine excretion is generally dependent on the THIOLA® dosage.

THIOLA® may be begun at a dosage of 800 mg/day in adult patients with cystine stones. In a multiclinic trial, average dose of THIOLA® was about 1000 mg/day. However, some patients require a smaller dose. In children, initial dosage may be based on 15 mg/kg/day. Urinary cystine should be measured at 1 month after THIOLA® treatment, and every 3 months thereafter. THIOLA® dosage should be readjusted depending on the urinary cystine value. Whenever possible, THIOLA® should be given in divided doses 3 times/day at least one hour before or 2 hours after meals.

In patients who had shown severe toxicity to d-penicillamine, THIOLA® might be begun at a lower dosage.

HOW SUPPLIED: THIOLA® (NDC 0178-0900-01), is available for oral administration as 100 mg. round, white, sugar coated tablets in bottles of 100 tablets each. Each tablet is imprinted in red with "M" on one side and blank on the other side. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].


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