THIOLA® (tiopronin)
Use in Pediatric Patients With Cystinuria

Summary

Prescribing Information

- THIOLA (tiopronin) immediate-release tablets are a reducing and cystine-binding thiol drug[1]
- The goal of therapy is to reduce urinary cystine concentration below its solubility limit. Tiopronin is an active reducing agent which undergoes thiol-disulfide exchange with cystine to form a mixed disulfide of tiopronin-cysteine. From this reaction, a water-soluble mixed disulfide is formed and the amount of sparingly soluble cystine is reduced[1]
- In an uncontrolled study of 66 patients with cystinuria age 9 to 68 years, adverse events (AEs) with an occurrence rate ≥5% included anemia, nausea, proteinuria, and rash[1]
- The recommended initial dosage in pediatric patients >20 kg is 15 mg/kg/day. Avoid dosages >50 mg/kg per day in pediatric patients. Pediatric patients receiving >50 mg/kg of tiopronin per day may be at increased risk for proteinuria[1]

Background

- Cystinuria is a genetic disorder that results in the formation of kidney stones and affects ~1 in 7,000 to ~1 in 10,000 people in the United States[2]
- Open-label studies have evaluated the safety and efficacy of tiopronin in pediatric patients with cystinuria and kidney stones:
    - Tiopronin was utilized post-surgery or alone as treatment for reduction of kidney stones and prevention of relapse[3]
    - Efficacy of tiopronin in combination with potassium citrate in the treatment of urinary abnormalities and prevention of kidney stone formation was assessed in pediatric patients with cystinuria[4]
    - Efficacy of tiopronin to prevent formation of kidney stones or reduce their number and dimensions was examined in children and young adults with cystinuria[5]
- In case studies, tiopronin was utilized in combination with standard of care as treatment for cystinuria in children aged 1-2 years[6]

Study Data

- Pediatric patients treated with tiopronin in combination with standard of care experienced reduction in cystinuria levels and a reduced number of kidney stones, in some cases without recurrence[3-5]
- Tiopronin appeared to be well tolerated and no serious AEs were reported[3,4]

Prescribing Information

- THIOLA (tiopronin) immediate-release tablets are a reducing and cystine-binding thiol drug for oral use. THIOLA is indicated, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine stone formation in adults and pediatric patients 20 kg and greater with severe homozygous cystinuria, who are not responsive to these measures alone[1]
- The goal of therapy is to reduce urinary cystine concentration below its solubility limit. Tiopronin is an active reducing agent which undergoes thiol-disulfide exchange with cystine to form a mixed disulfide of tiopronin-cysteine. From this reaction, a water-soluble mixed disulfide is formed and the amount of sparingly soluble cystine is reduced[1]
- AEs occurring at an incidence of ≥5% in an uncontrolled trial in 66 patients with cystinuria age 9 to 68 years are shown in **Table 1**. Patients in group 1 had previously been treated with d-penicillamine; those in group 2 had not. Of those patients who had stopped taking d-penicillamine due to toxicity (34 out of 49 patients in group 1), 22 were able to continue treatment with THIOLA. In those without prior history of d-penicillamine treatment, 6% developed reactions of sufficient severity to require THIOLA withdrawal[1]

Table 1. Adverse Reactions Occurring in One or More Patients

System Organ Class	Adverse Reaction	Group 1 Previously Treated With d-penicillamine (n=49)	Group 2 Naive to d-penicillamine (n=17)
Blood and Lymphatic System Disorders			
	anemia	1 (2%)	1 (6%)
Gastrointestinal Disorders			
	nausea	12 (25%)	2 (12%)
	emesis	5 (10%)	–
	diarrhea/soft stools	9 (18%)	1 (6%)
	abdominal pain	–	1 (6%)
	oral ulcers	6 (12%)	3 (18%)
General Disorders and Administration Site Conditions			
	fever	4 (8%)	–
	weakness	2 (4%)	2 (12%)
	fatigue	7 (14%)	–
	peripheral (edema)	3 (6%)	1 (6%)
	chest pain	–	1 (6%)
Metabolism and Nutrition Disorders			
	anorexia	4 (8%)	–
Musculoskeletal and Connective Tissue Disorders			
	arthralgia	–	2 (12%)
Renal and Urinary Disorders			
	proteinuria	5 (10%)	1 (6%)
	impotence	–	1 (6%)
Respiratory, Thoracic and Mediastinal Disorders			
	cough	–	1 (6%)
Skin and Subcutaneous Tissue Disorders			
	rash	7 (14%)	2 (12%)
	ecchymosis	3 (6%)	–
	pruritus	2 (4%)	1 (6%)
	urticaria	4 (8%)	–
	skin wrinkling	3 (6%)	1 (6%)

- AEs have also been reported during post-approval use of THIOLA (**Table 2**). Because post-approval reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to THIOLA exposure[1]

Table 2. Adverse Reactions Reported for THIOLA Pharmacovigilance by System Organ Class and Preferred Term

System Organ Class	Preferred Term
Cardiac Disorders	congestive heart failure
Ear and Labyrinth Disorder	vertigo
Gastrointestinal Disorders	abdominal discomfort; abdominal distension; abdominal pain; chapped lips; diarrhea; dry mouth; dyspepsia; eructation; flatulence; gastrointestinal disorder; gastroesophageal reflux disease; nausea; vomiting; jaundice; liver transaminitis
General Disorders and Administration Site Conditions	asthenia; chest pain; fatigue; malaise; pain; peripheral swelling; pyrexia; swelling
Investigations	glomerular filtration rate decreased; weight increased
Metabolism and Nutrition Disorders	decreased appetite; dehydration; hypophagia
Musculoskeletal and Connective Tissue Disorders	arthralgia; back pain; flank pain; joint swelling; limb discomfort; musculoskeletal discomfort; myalgia; neck pain; pain in extremity
Nervous System Disorders	ageusia; burning sensation; dizziness; dysgeusia; headache; hypoesthesia
Renal and Urinary Disorders	nephrotic syndrome; proteinuria; renal failure
Skin and Subcutaneous Tissue Disorders	dry skin; hyperhidrosis; pemphigus foliaceus; pruritus; rash; rash pruritic; skin irritation; skin texture abnormal; skin wrinkling; urticaria

- Monitoring of patients taking THIOLA includes[1]:
  - Measurement of urinary cystine 1 month after starting THIOLA and every 3 months after. THIOLA dosage should be adjusted to maintain urinary cystine concentration <250 mg/L
  - Assessment for proteinuria before treatment and every 3 to 6 months during treatment
  - Discontinuation of THIOLA in patients who develop proteinuria and monitoring of urinary protein and urinary function. After resolution of proteinuria, restarting THIOLA at a lower dose can be considered

Background

Cystinuria Disease State

Cystinuria is a genetic metabolic disorder that disrupts transport of dibasic amino acids in the proximal tubules of the kidney.[2,7] Cystinuria is characterized by excessive urine levels of cystine, arginine, lysine, and ornithine. Concentrations of cystine in excess of 250 mg/L in the urine can lead to formation of crystals and calculi (stones) in the kidney, bladder, and ureters. Due to the low solubility of cystine in urine, patients may develop hundreds of stones per year; severe cases bring about an increased risk of developing hypertension, chronic kidney disease, and end-stage kidney

disease.[2,7] Cystinuria occurs in both adults and children and affects males and females in equal numbers. Symptoms typically begin between ages 10 and 30 years, with mean age of first presentation of 12 to 13 years.[2,7]

The primary objective of treatment for cystinuria is the reduction of urinary cystine. A multifaceted approach to treatment may decrease urinary cystine and prevent cystine stone formation.[2]

This includes daily consumption of large amounts of fluid to increase urine volume and decrease cystine levels, alkalization of urine with potassium citrate and acetazolamide to increase dissolution of cystine, and further alkalization by modifications in dietary salt and animal protein intake.[2] Specifically, it is recommended that patients[8]:

- maintain a daily fluid intake of 4 L in order to dilute urinary cystine and achieve a targeted minimum urine output of 2.5 L/day
- maintain a urine pH level of 7.0 by taking potassium alkali
- maintain a diet low in animal protein and restrict sodium intake to ≤2300 mg/day

Open-Label Studies

Treatment of pediatric patients with tiopronin has also been assessed in open-label studies. Studies varied with regard to duration, patient age, tiopronin dosage, and outcome measures. [3-5]

Case Studies

Case studies of tiopronin treatment for pediatric patients with acute kidney injury caused by bilateral obstructive nephrolithiasis have been reported. Tiopronin therapy was initiated following surgical interventions.

Study Data

Open-Label Studies

In a study of children aged 20 months to 11 years, tiopronin was utilized post-surgery (n=6) or alone (n=1) as treatment for the reduction of kidney stones and prevention of relapse. The initial tiopronin dose was 10 mg/kg/day and was increased to achieve a cystinuria level <200 mg/day. Urine alkalization (pH=6.5-7.0) was maintained by use of sodium bicarbonate and a high daily fluid intake was recommended. In 6 cases, plain film X-ray was conducted every 6 months to evaluate size and location of kidney stones. Mean follow up was 3 years (range, 11 months to 5 years 5 months).[3]

In 5 of 7 children aged 20 months to 11 years, tiopronin in combination with alkalization therapy and high fluid intake was effective in decreasing cystinuria and reducing the size and number of kidney stones Length of treatment varied, with a range of 21 to 65 months (mean, 40 months). Pre-treatment cystinuria ranged from 170 to 716 mg/day (mean, 382 mg/day); during treatment, the observed range was 76 to 716 mg/day (mean, 222 mg/day). Final recommended tiopronin dose was 20 to 50 mg/kg/day, with adjustments according to cystinuria levels in 24-hour collections.[3]

Development of kidney stones varied across subjects. Patient 1 did not undergo surgery and experienced a reduction in the number of calculi. Patient 2 experienced disappearance of calculi 4

months post-surgery. Patients 3, 4, and 5 had no stone recurrence. Stone recurrence was reported in patients 6 and 7. Patient 6 was lost to follow up for 3 years, during which the parents reduced tiopronin dose to 5 mg/kg/day. Upon reobservation, the patient presented with an elevated cystinuria level (716 mg/day) and unilateral kidney stones. Patient 7 showed calculi development 5 months post-surgery, possibly in part due to inadequate fluid intake. The patient underwent a second surgery, after which tiopronin dose was increased from 20 mg/kg/day to 40 mg/kg/day. No stone recurrence occurred 12 months after the second surgery.[3]

Adverse events included temporary impaired sense of taste (n=1), mild diarrhea (n=1), and nephrotic syndrome (n=2). Symptoms abated upon tiopronin dose reduction or withdrawal, and did not return upon drug re-challenge.[3]

A second study evaluated the effect of combined increased fluid intake, tiopronin, and potassium citrate in the prevention of kidney stones, reduction of urinary cystine excretion, and increase in urinary pH and citrate excretion. Patients included 13 boys and 5 girls aged 1 to 16 years (median, 6.5 years) with documented cystine calculi. At baseline, serum creatinine was <1 mg/dL and endogenous creatinine clearance was ≥50 mL/min.[4]

Prior to treatment with tiopronin, 4 patients experienced spontaneous passage of kidney stones. Stone removal interventions among patients included open surgery, percutaneous nephrolithotripsy, extracorporeal shock wave lithotripsy with or without additional intervention, and ureteroscopy. Medical treatment was initiated following stone removal, comprised of fluid intake >40 mL/kg body weight/24 hours, 1 mEq/kg/g daily potassium citrate in a 1 mEq/mL solution or 5 mg wax matrix, and 10 to 15 mg/kg/day tiopronin. Potassium citrate dose was adjusted to maintain urinary pH of 6.5 to 7.5. Potassium citrate and tiopronin were given in 3 divided doses.[4]

Patients were followed every 3 months for the first 6 months, then every 6 months. Laboratory assessments and stone recurrence, defined as radiological appearance or passage of a nonpre-existing stone or documented stone growth, were evaluated at each visit. High-resolution lipid chromatography was conducted in a subsample of patients (n=9) to determine quantitative cystine.[4]

In 18 children aged 1 to 16 years with confirmed cystine calculi, tiopronin was added to standard of care for the prevention of kidney stones, reduction of urinary cystine excretion, and increase in urinary pH and citrate excretion. Fifteen patients were followed for 3 to 35 months (median, 15 months). During follow up, 10 patients (66.7%) were stone-free; 8 stones recurred in the other 5 patients. The overall recurrence rate was 0.64 per patient year. There was poor association between urinary cystine excretion and disease course. Among patients with recurring calculi, 80% experienced 2.4 to 3.1-fold reduction in urinary cystine compared to baseline.[4]

High-resolution lipid chromatography was conducted in 9 patients; urinary citrate excretion and pH increased significantly in 8 patients after treatment compared to baseline (P=0.015). All patients achieved normal urinary citrate excretion (**Table 3**). However, compared to healthy controls, urinary cystine levels remained higher than the normal upper limit in all patients despite the combined therapeutic approach.[4]

Table 3. Medical Treatment and 24-hour Urinary Changes

	Median ± SD		p value
	Pre-treatment	Post-treatment	
Urinary pH	5.6 ± 0.2	6.9 ± 0.3	0.020
Cystine (mmol/mol creatinine)	245 ± 233	140 ± 106	0.015
Citrate (mg/1.73/m^2)	255 ± 219	729 ± 494	0.003

Wilcoxon signed rank test compared baseline values with those of treatment.
Adapted from Tekin et al. *J Urol*. 2001;165(6 Pt 2):2328-2330.

There were no serious adverse events associated with tiopronin or potassium citrate treatment.[4]

Additional research examined long-term treatment to prevent formation of kidney stones or reduce their number and dimensions in children and young adults aged 1.8 to 24 years (mean, 12.6 years) with confirmed cystinuria. Cystinuria was defined as cystine excretion >300 µmol/mmol of creatinine in patients with a history of ≥1 cystine renal stone. Twenty patients were enrolled into the study; patient histories were reviewed for stone episodes, defined as spontaneous kidney stone emissions and/or surgical procedures in the 3 years prior to the study. At baseline, 11 patients presented with ≥1 kidney stone; 6 patients were stone-free due to prior surgical removal. One patient did not have a stone episode in the 3 years prior to the study, but did have a history of kidney stones.[5]

Treatment included alkalization with either potassium citrate (n=10) or sodium bicarbonate (n=9) to raise urine pH (7.0-8.0). Patients were instructed to drink ≥1 L of water/m^2 of body surface area and conduct weekly dipstick tests to measure urine pH and proteinuria. Patients were treated with cystine-binding drugs (tiopronin, n=16, or D-penicillamine, n=2); dosages were adjusted to keep a target level of urine free-cystine <100 µmol/mmol creatinine. Mean dose of tiopronin was 24.65 mg/kg/day (range, 13.8 to 51 mg/kg/day). Free and drug-bound urine cystine levels were determined separately in morning urine samples every 4 to 6 months via derivatization and chromatography procedures; renal stones were monitored by ultrasound every 4 to 6 months.[5]

Eighteen pediatric patients were treated with the combination of standard of care plus cystine-binding medication (tiopronin, n=16, or D-penicillamine, n=2). Patients were followed for 12 to 86.4 months (mean, 42 months; median, 36 months). All patients who completed the study (n=18) achieved free-cystine levels below target (<100 µmol/mmol creatinine); this finding was observed in 79% of determinations. In most patients, free-cystine level was <50 µmol/mmol in ≥35% of determinations. Stone episodes at baseline equaled 0.28/year and decreased to 0.03/year once free-cystine target level was achieved. Six patients experienced reduction in the number and dimensions of pre-existing stones (**Table 4**). Surgical intervention for stone removal was needed in 1 subject; no stone occurrence was observed after 12 months of medical treatment.[5]

Table 4. Details of Renal Stone Evolution in the 6 Patients Who Had Stones at the Onset of the Study and Who Improved During Follow Up

Renal stones at start of study				Renal stones at last observation			
Right kidney		Left kidney		Right kidney		Left kidney	
Number of stones	Largest stone dimension	Number of stones	Largest stone dimension	Number of stones	Largest stone dimension	Number of stones	Largest stone dimension
4	4 mm	2	12 mm	No stones		2	8 mm
Multiple	4 mm	Multiple	3 mm	Rare	1-2 mm	Rare	1-2 mm
3	2 mm	3	2-3 mm	No stones		No stones	
1	11 mm	Several	1-3 mm	No stones		No stones	
2	3 mm	5	8 mm	No stones		4	6 mm
2	10 mm	1	Staghorn	2	5 mm	1	13 mm

Adapted from Dello Strologo et al. *Pediatr Nephrol.* 2007;22(11):1869-1873.

After 6 years of tiopronin treatment, 1 patient developed proteinuria and was withdrawn from the study. No stones occurred during the treatment period. Five months after study withdrawal, the patient experienced new stone occurrence.[5]

Case Studies

A 2-year-old girl with renal failure, hyperkalemia, and metabolic acidosis was diagnosed with bilateral kidney stones with accompanying cystinuria, hyperoxaluria, and hypocitraturia. The patient underwent ureteral stent insertion followed by ureteroscopy and percutaneous nephrolithotomy. Cystinuria was diagnosed following surgery; treatment with potassium citrate was initiated and high fluid intake was recommended. Additional surgery revealed a cystine stone; tiopronin was added as supportive care and the patient remained stone-free at 12 months follow up.[6]

A 1-year-old girl with persistent oliguria and vomiting presented with bilateral kidney stones and high urinary cystine. Potassium citrate was prescribed and high fluid intake was recommended. The patient underwent 2 percutaneous nephrolithotomy operations. Stone analysis revealed 3 stones and tiopronin therapy was initiated. At 5 months of treatment, serum creatinine levels were found to be normal.[6]

Safety

American Urological Association guidelines noted that tiopronin may cause elevations in liver enzymes and induce anemia and other hematologic abnormalities, and recommended that clinicians obtain periodic blood tests to assess for adverse reactions.[8]

References

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