

NEPHROTIC SYNDROME INDUCED BY TIOPRONIN IN A MALE PATIENT WITH CYSTINURIA

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ABSTRACT

Cystinuria is a rare, lifelong, autosomal recessive disorder characterized by high urine cystine excretion, leading to chronic and recurrent kidney stone formation. This inherited metabolic disorder occurs due to defective cystine, lysine, ornithine, and arginine reabsorption in the brush border membrane of the proximal renal tubule (S3 segment) and the gastrointestinal epithelial cells. Tiopronin is a thiol agent used in the treatment of severe homozygous cystinuria in patients who are resistant to conservative measures. We report an 18-year-old male with cystinuria confirmed by genetic testing, who was treated with conservative measures such as high fluid intake, low sodium diet, and oral potassium citrate since the diagnosis was made at four years of age. However, due to the recurrence of several calculi in both kidneys, tiopronin treatment was initiated at the dose of 250 mg three times a day. After three months of therapy, the patient developed nephrotic syndrome with proteinuria of 6.6 g/l, hypoproteinemia, hyperlipidemia, and edema. Considering the adverse effect of tiopronin, the drug was immediately withdrawn and the patient was managed with human albumin substitution, diuretics, and angiotensin receptor blocker, without corticosteroids. Complete clinical and biochemical remission was achieved within 7 days. Clinicians should be aware of

this rare but serious adverse effect of tiopronin, and monitor patients receiving tiopronin carefully for the possible occurrence of edema, proteinuria, with the aim of timely intervention and tiopronin discontinuation.

Keywords: Cystinuria, tiopronin, adverse drug reaction, nephrotic syndrome

INTRODUCTION

Cystinuria (OMIM 220100) is a rare, lifelong autosomal recessive disorder characterized by high urine cystine excretion, leading to chronic and recurrent kidney stone formation. This inherited metabolic disorder occurs due to defective amino acids (cystine, lysine, ornithine, and arginine) reabsorption in the brush border membrane of the proximal renal tubule (S3 segment) and the gastrointestinal epithelial cells [1]. The defective reabsorption is primarily caused by mutations in the *SLC3A1* or *SLC7A9* genes identified by the International Cystinuria Consortium (ICC), which encode components of the amino acid transport system. The transport proteins rBAT (encoded by *SLC3A1*) and b (0, +) AT (encoded by *SLC7A9*) participate in affinity transport of cystine and dibasic amino acids in the kidney and intestine by forming a heterodimeric transport network connected by a covalent disulfide bond [2]. Inefficient reabsorption of cystine leads to its accumulation in urine, where its low solubility in acid urine (pH<7.0) contributes to precipitation and the formation of cystine stones [2].

Cystinuria is inherited in autosomal recessive fashion – results from biallelic pathogenic variants, usually inherited from typically healthy carrier parents. This genetic mechanism underscores the importance of genetic counseling for at-risk families. There are two types of cystinuria: Type A results from biallelic pathogenic *SLC3A1* variants (chromosome 2p21), and type B results from biallelic pathogenic

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SLC7A9 variants (chromosome 19q13.11). Healthy carriers of type A cystinuria (parents or some of the siblings) always have a normal excretion of amino acids in the urine, while type B carriers have a high urinary excretion of cystine and dibasic amino acids in over 80% of cases, but usually do not produce stones or produce them episodically [3]. According to clinical data, males experience more severe form of the disease than females [4]. Cystinuria poses management challenges with recurrent urinary stones, but if treated appropriately it has a good prognosis. Tiopronin (2-mercapto-propionylglycine) is a prescription thiol drug used primarily in the treatment of severe homozygous cystinuria. Tiopronin is used as a second-line therapy to control the rate of cystine precipitation and excretion, and prevent kidney stone formation. It is used after a failure of the non-pharmacological first-line treatment consisting of increased fluid intake, restriction of sodium and protein, and urinary alkalization [5]. Some adverse effects have been reported for tiopronin, including cutaneous side effects (pruritus, erythema, and pemphigus), agranulocytosis, obliterating bronchiolitis, and nephrotic syndrome [5]. Here, we report a case of tiopronin-induced nephrotic syndrome.

CASE PRESENTATION

An 18-years old male was referred for review at our department due to bilateral lower limb edema and rapid weight gain in the preceding two weeks. At the age of 4, the patient was diagnosed with cystinuria, following recurrent renal stones that required multiple lithotripsy sessions. The diagnosis was suggested by high urinary content of cystine and dibasic amino acids (cystine:creatinine ratio was 299 mmol/mmol; referent values <20). Genetic testing identified two *SLC3A1* pathogenic variants R365L, inherited from the mother, and M467T, inherited from the father in trans phase (compound heterozygote). The patient was treated with conservatively with high fluid intake, low sodium diet, and oral potassium citrate 0.1 g/kg/day for 14 years. However, due to the recurrence of several calculi in both kidneys, three months before admission to our hospital, the patient

was started on therapy with tiopronin (250 mg three times a day). Initial laboratory investigations revealed nephrotic syndrome, with proteinuria of 6.6 g/l (normal < 0.1 g/l) and serum creatinine level of 79 µmol/l (normal 45-109 µmol/l) (Table 1). Therapy with tiopronin was stopped, and the patient was managed conservatively with salt restriction, intravenous human albumin infusions, low dose of angiotensin 2 receptor blocker and diuretics. Ultrasound examination showed tri calculi in the right kidney and one small calculus in the left kidney without hydronephrosis. A kidney biopsy was not performed. Complete clinical and biochemical remission was achieved within 7 days, with a 12 kg decrease in body weight, reduction in the 24-hour proteinuria to 0.18 g/l and normal serum proteins level. Steroids were not used, as proteinuria resolved promptly and effectively after discontinuing tiopronin. The treatment was continued with alkali treatment with oral potassium citrate, conservative measures of high fluid intake and diet modification.

DISCUSSION

Since the 1980s, tiopronin has been effectively used in the treatment of severe homozygous cystinuria, in patients who are resistant to conservative measures of high fluid intake, alkali and diet modification (in-label indication), as well as in rheumatoid arthritis (off-label indication) [6]. Furthermore, tiopronin has been widely utilized in China to treat chemotherapy-related liver toxicity, viral hepatitis, and fatty liver disease [7,8,9]. In patients with cystinuria, the thiol group of tiopronin reacts with the disulfide bonds of cystine (composed of two cysteine molecules) and forms mixed disulfide of tiopronin-cysteine which increases solubility and reduces the risk of forming new cystine stones and dissolving of previously formed ones [6,7]. The side effects of tiopronin are usually mild and include cutaneous diseases (pruritus, erythema, pemphigus), stomatitis, gastrointestinal problems (vomiting, abdominal pain, diarrhea, ageusia) and transitory hematological abnormalities (leucopenia, thrombocytopenia). Nephrotic syndrome is a rare, but serious adverse effect of tiopronin [5-7].

Table 1. Laboratory parameters during the treatment and follow-up of the patient

Laboratory parameter	On admission	7 th day of hospitalization	After one month
24 hours proteinuria (normal < 0.1 g/l)	6.6 g/l	0.18 g/l	0.2 g/day
Serum albumin (normal 35-50 g/l)	19 g/l	31 g/l	49 g/l
Total proteins (normal 63-83 g/l)	41 g/l	56 g/l	73 g/l
Total cholesterol (normal < 5.17 mmol/l)	6.6 mmol/l	4.8 mmol/l	3.76 mmol/l
Serum creatinine (normal 45-109 µmol/l)	75 µmol/l	71 µmol/l	73 µmol/l

In a large retrospective analysis of 442 patients with cystinuria in France, 30.1% (n=133) of the patients were treated with tiopronin. The majority of the patients (69.9% or 93 patients) did not have any adverse events, proteinuria was noted in 10 patients (7.5%), gastrointestinal AEs in 10 patients (7.5%), cutaneous AEs in 13 patients (9.7%), hematological AEs in 6 patients (4.5%) and mouth sore-ness was reported in 1 patient (0.75%). Proteinuria was also noted in 30.8% of patients who were treated with D-penicillamine, and in none of the patients treated only with alkalinizing therapy. More patients experienced at least one AE during treatment with D-penicillamine compared to tiopronin, but the difference was not significant. Tiopronin-related AEs required less treatment discontinuations and more dose reductions than AEs associated with D-penicillamine, which indicates that the overall safety of tiopronin might be slightly better than that of D-penicillamine. Discontinuation of treatment leads to favorable outcomes in more than 96% of patients with AEs due to tiopronin [10]. In addition, when it comes to alternative

treatment options for cystinuria, D-penicillamine is a β -dimethyl analog of cysteine and first-generation thiol that is available to patients unable to tolerate tiopronin. However, D-penicillamine is generally less well tolerated than tiopronin. In fact, up to 84% of patient on this D-penicillamine experience significant side effects and approximately 70% ultimately discontinue it [10]. Since thiol medications can have intolerable side effects, there can be decreased medication adherence amongst cystinuria patients. Such effects include nausea, diarrhea, altered taste perception, fever, nephrotic syndrome, dermatitis, arthropathy, myalgia, muco-cutaneous lesions, pancytopenia, and zinc and copper deficiencies [2,10]. Furthermore, long-term use of D-penicillamine can cause vitamin B6 deficiency, requiring pyridoxine supplementation. Consequently, patients taking this medication require close monitoring of renal function, blood counts, liver function, and mineral levels [2,10].

Other authors also described nephrotic syndrome in patients with cystinuria treated with tiopronin, and the

Table 2. Reported cases of Tiopronin-induced nephrotic syndrome in patients with cystinuria

Authors	Age (years)	sex	Dosage	Occurrence time after initiation of tiopronin	Clinical presentation	Renal biopsy findings	Therapy	Outcome
Our case	18	male	10 mg/kg/day	3 months	nephrotic syndrome with proteinuria of 6.6 g/l	No	tiopronin withdrawal	complete remission after 7 days
Tasic V et al (2011) ¹⁶	3	male	10 mg/kg/day	9 months	nephrotic syndrome	No	tiopronin withdrawal	complete remission after 10 days
Vidović L et al (2021) ⁵	22	female	no data	4 months	nephrotic syndrome with proteinuria of 4.4 g/day	acute interstitial nephritis	tiopronin withdrawal and prednisone 60 mg	remission with proteinuria 0.4 g/24 h after 7 days
Iwanaka Y et al (2024) ¹⁸	13	female	9.1 mg/kg/day	44 months	nephrotic syndrome	No	tiopronin withdrawal	complete remission after 10 days
Kalbani Al et al (2020) ¹⁹	13	male	12 mg/kg/day	3 months	nephrotic syndrome	No	tiopronin withdrawal	complete remission after 1 month
Micallef S et al (2022) ²⁰	16	male	12 mg/kg/day	16 months	acute kidney injury and nephrotic syndrome with proteinuria 6 g/day	membranous nephropathy, likely drug-induced.	tiopronin withdrawal	serum creatinine dropped to 117 μ mol/l and albumin:creatinine ratio to 47.7 mg/g (normal range 1–20 mg/g) within 2 months
Lecoules S et al (1999) ²¹	73	male	no data	6 weeks	severe nephrotic syndrome	minimal glomerular lesions	tiopronin withdrawal	complete remission 5 weeks after withdrawal
Shibasaki T et al (1990) ²²	26	male	no data	36 months	nephrotic syndrome	membranous glomerulonephritis (MN) at stage I	tiopronin withdrawal and prednisone	complete remission
Yamashita J et al (2024) ¹⁴	41	female	600-1600 mg/day	6 months	nephrotic syndrome with proteinuria of 5.5 g/gCre (normal < 0.2 g/gCre)	membranous nephropathy with strong deposition of immunoglobulin G4	tiopronin withdrawal	remission after 1 year. After 5 years tiopronin was reintroduced, nephrotic syndrome appeared again, and tiopronin was stopped with remission after 6 months
Santoriello D et al (2023) ¹⁵	53	male	no data	7 months	nephrotic syndrome with proteinuria of 4.6 g/day and slightly elevated serum creatinine	Segmental membranous nephropathy, NELL-1 positive	tiopronin withdrawal, telmisartan and dapagliflozin	After 6 months normal serum creatinine and albumin, but a protein-to-creatinine ratio of 2.08 g/g (patient with diabetes, obesity)

clinical summaries are presented in Table 2. Interestingly, the time to onset of nephrotic syndrome after initiating treatment with tiopronin varied from 3 to 44 months, and showed no association with the dose, age or sex. Complete recovery was usually achieved a few weeks after tiopronin withdrawal (Table 2).

The mechanism through which tiopronin induces nephrotic syndrome in patients with cystinuria is not fully understood. It is believed that tiopronin might interfere with glomerular function via series of immune-mediated processes (hypersensitivity, immune complex deposition with activation of complement system and inflammation), direct podocytes injury (toxicity of tiopronin metabolites), increased oxidative stress and alteration in the glomerular basal membrane [6]. Genetic susceptibility for proteinuria was suggested by association with HLA-B35-Cw4 and HLA-DR3 alleles [11,12]. Both HLA-B35-Cw4 and HLA-DR3 alleles might contribute to a heightened or altered immune response, potentially leading to chronic inflammation in the kidneys. This inflammation could damage the glomeruli (filtering units of the kidneys), allowing proteins to leak into the urine. When it comes to alteration in the glomerular basal membrane, mutations in mouse laminin-11 have been reported to result in nephrotic syndrome suggesting an important role of this protein for normal glomerular filtration. More recently a few other proteins, both intra- and extra-cellular, have been shown to form part of a protein complex that contributes to the slit diaphragm structure. Mutations in any of these proteins lead to nephrotic syndrome [13]. In the case study of Ferraccioli *et al.* four of six biopsies in patients with tiopronin-induced nephrotic syndrome showed membranous glomerulonephritis, and one patient each with mesangia proliferative and segmental mesangial deposits [11]. However, membranous glomerulonephritis in these patients might show negative staining for IgA and IgM on immunofluorescence (IgA, IgM, and C1q deposits are suggestive of secondary membranous glomerulonephritis), selective IgG3 deposits and unusual positive staining for IgG4 which is suggestive of idiopathic membranous glomerulonephritis.[14] Tiopronin-induced membranous glomerulonephritis could be positive for neural epidermal growth factor-like 1 protein (NELL-1) on immunohistochemistry. [15] Cases of tiopronin-associated minimal change disease and acute interstitial nephritis were also documented. [5,6]

Our patient presented with severe nephrotic syndrome 3 months after initiation of tiopronin at the dose of 10 mg/kg/day. Based on data from the literature and a previously described similar case by one of the authors [16], renal biopsy was not performed, and the nephrotic syndrome was considered a side effect of tiopronin use. Tiopronin was

immediately discontinued and the patient was treated with restriction of salt and water, and careful use of diuretics and alkalizing agents (sodium bicarbonate and potassium citrate). Complete remission was achieved within 7 days of tiopronin withdrawal. Given there are no clear guidelines related to management of tiopronin-induced nephropathy the questions concerning further patient treatment including whether tiopronin can be re-introduced remain open. *Rizzoni et al.* described two cases of cystinuria in which a nephrotic syndrome developed during treatment with tiopronin; symptoms resolved after withdrawal of the drug and did not recur when the tiopronin was given again in lower doses. The dose of 50 mg/kg per day was considered the threshold for triggering of nephrotic syndrome. [17] However, the dose of tiopronin (10 mg/kg/day) given to our patient was far lower than this threshold. In the case of *Yamashita J et al.* tiopronin was reintroduced after five years, but the patient developed nephrotic syndrome again and the drug was permanently withdrawn.[14] The cross-reactivity between tiopronin and D-penicillamine was small, so it is suggested that they could probably be used interchangeably in case of side effects caused by one of them [10].

Invasive renal biopsy is unlikely to provide further relevant information about the mechanisms of the tiopronin-induced nephropathy, given primary renal disease or predisposition is unlikely. Additional testing for serum anti-PLA2R antibodies and HLA typing may provide broader explanation of the condition.

CONCLUSION

We present a patient with cystinuria and tiopronin-induced nephrotic syndrome, who underwent complete remission 7 days after withdrawal of tiopronin. It is likely that tiopronin causes reversible damage of the podocytes, resulting with complete remission and excellent prognosis quickly after discontinuing of tiopronin. Clinicians should be aware of this rare but serious adverse effect of tiopronin, and therefore, patients receiving tiopronin should be counselled to monitor for edema and should be carefully monitored for proteinuria, with the aim of timely intervention and tiopronin discontinuing. Of course, generalization is difficult or impossible, taking in consideration that we need both a cause-effect relationship and a representative population for which the findings are valid.

STATEMENTS AND DECLARATIONS

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Competing interests

The authors declare no competing interests and have no financial interests to declare

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