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The purpose of this study was to summarize 14 years of clinical experience with medical treatment of 88 cystinuric dogs. Of special interest was evaluation of recurrence rate of cystine uroliths and adverse effects during long-term tiopronin treatment. Twenty-six different breeds were recognized, and the most common breeds were Dachshunds, Tibetan Spaniels, and Basset Hounds. In 76 of 88 treated dogs (86%), re-formation of cystine uroliths was prevented. Recurrence rate of cystine uroliths changed from 7 months before to 18 months during tiopronin treatment. On 28 occasions, bladder stones were found, and in about 60% of the dogs, the uroliths dissolved. Quantitative measurement of the urinary excretion of cystine showed a significantly ($P < .03$) higher excretion of cystine in dogs with recurrent urolith formation than in dogs with only 1 urolith episode. Another finding was a significant ($P = .02$) decrease in urinary cystine excretion in older (>5 years) than in younger (<5 years) dogs. Adverse effects were found in 11 dogs, and the most severe signs were aggressiveness and myopathy. All signs disappeared when tiopronin treatment was stopped. In conclusion, this study emphasizes the importance of an individual strategy for lifelong treatment of cystinuria. In addition to increasing water intake, chemical modification of the cysteine molecule into a more soluble form by means of tiopronin is useful. In dogs with re-formed cystine uroliths, dissolution may be induced by increasing the tiopronin dosage to 40 mg/kg body weight per day. In dogs with a low urolith recurrence rate and low urinary cystine excretion, the tiopronin dosage may be decreased or treatment discontinued.

Key words: Cystinuria; Dibasic amino acids; Tiopronin; Urolithiasis.

Cystinuria is a disease in which increased amounts of the amino acid cystine, and to a variable extent lysine, arginine, and ornithine, are excreted in the urine.[1,2] The solubility of cystine in urine is low; therefore, dogs with cystinuria are predisposed to urolith formation.[3–5] Investigations have shown that cystine uroliths account for 1–22% of uroliths in the dog, with higher occurrence in European countries such as Germany and Sweden than in the United States.[6–8]

The disease has been reported in many breeds but most frequently in the Dachshund, Basset Hound, Irish Terrier, and English Bulldog, and it is most commonly found in males.[6–8]

For detection of cystinuria, analysis of urinary calculi and identification of hexagonal urinary crystals or a positive cyanide nitroprusside reaction of urine may be helpful.[9] For diagnosis, quantitative measurements of urinary cystine excretion by ion exchange chromatography can be used.[10]

Canine cystinuria appears to be a heterogeneous disease. Isolated cystinuria combined with lysinuria have been reported by some investigators,[5,11] and the full pattern of cystine and the 3 dibasic amino acids appearing in excess in the urine have been reported by other investigators.[2,12,13]

The mode of inheritance of cystinuria has been investigated. In humans, 3 types of cystinuria have been identified, probably reflecting different alleles.[14] More recently, the amino acid transport gene SLC3A1 (former rBAT gen) located on chromosome 2 has been described in detail.[15–17] Mutations in that gene have been shown to be associated with cystinuria and probably represent the pathogenic background of the classic form (type 1) of the disease in humans. Furthermore, recent investigations in humans indicate that there is a nontype 1 cystinuria caused by mutations in another gene (SLC7A9) encoding a subunit of SLC3A1 located on chromosome 19.[18] Mutations in this 2nd cystinuria gene (SLC7A9) have been shown to cause the incompletely recessive form of cystinuria (types II and III).[19]

In studies of Newfoundland dogs, clinical signs of urinary obstruction occur in male and female offspring from noncystinuric parents, and observations consistent with an autosomal recessive mode of inheritance were made.[20] The molecular basis of cystinuria has been further investigated in Newfoundland dogs, and the cloning and sequencing of the canine SLC3A1 gene and identification of a nonsense mutation in exon 2 of the gene have been made.[21]

However, in cystinuric dogs of 6 other breeds (Welsh Corgi, Dachshund, Pointer, Irish Setter, Jack Russell Terrier, and Swedish Lapphund), either heterozygosity at the SLC3A1 locus or lack of mutations in the coding region of the SLC3A1 gene were observed, indicating that cystinuria is genetically heterogeneous in dogs, as in humans.[21]

After surgical removal, recurrence of cystine uroliths within 1 year is common because of the inborn renal tubular defect.[7,22] Therefore, there is a need to find an effective strategy for treatment that provides medical dissolution of uroliths and prophylactic therapy to prevent renewed urolith formation. Without such a strategy, many owners may resort to euthanasia instead of further surgical intervention.

Different therapeutic approaches have been described over the years, such as dietary changes, induced diuresis, increase of cystine solubility by inducing an alkaline urinary pH, and conversion of cystine to a more soluble compound with D-penicillamine or tiopronine.

Attempts have been made in humans to design diets low in methionine and decrease the excretion of cystine. The effects of such diets have been variable. Some investigators

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have found that a diet low in methionine results in a marked decrease in urinary cystine excretion,[23] but other workers have not been able to confirm this finding.[24] Further studies in humans have concluded that tubular reabsorption of cystine in patients with cystinuria can be increased by dietary sodium restriction.[25–27] The mechanisms suggested by Peces et al[27] are that reduced sodium intake causes increased sodium reabsorption in the proximal tubules, which in turn increases the transport of cystine across the luminar tubular cell membrane. It has been suggested that this phenomenon can be utilized in the treatment of cystinuria to reduce urinary excretion of cystine by means of a low sodium diet.[27,28]

The introduction of the thiol-containing drugs penicillamine and tiopronin[a] made it possible to further reduce the urinary cystine concentration.[7,29–31] Although D-penicillamine is effective in preventing the formation of cystine uroliths and sometimes in the dissolution of them, this treatment is accompanied by frequent complications, such as vomiting, that limit its use in dogs.[22] Another property of penicillamine is its chelation of metals. This effect has been utilized in the treatment of hepatic copper toxicosis but must be considered a potential adverse effect in treatment of cystinuria because studies have shown increased urinary excretion of calcium, copper, and zinc after oral treatment of dogs with penicillamine.[32] Treatment with tiopronin is not associated with as many adverse effects, and tiopronin does not possess chelation properties with metals such as calcium, copper, zinc, magnesium, chromium, cobalt, and iron.[32] Furthermore, tiopronin has higher oxidation-reduction potential than penicillamine and may be even more effective in a disulfide exchange reaction.[33]

The purpose of the present study was to evaluate 14 years of medical treatment of cystinuric dogs. Of special interest is evaluation of the recurrence rate of cystine uroliths and adverse effects during long-term tiopronin treatment. An individual scheme for management of the cystinuric dog also is presented.

Materials and Methods

Dogs and Design of the Study

Eighty-eight male cystinuric dogs were treated with tiopronin from 1986 to 2000. Fifty dogs were treated at the Department of Small Animal Clinical Sciences in Uppsala. Thirty-eight dogs were handled by consultations with the University Clinic in Uppsala and treated by use of the same principles as used at the university, by veterinarians at different animal hospitals in Sweden. The diagnosis in all dogs was made before this study started and was based on infrared spectroscopy of surgically removed uroliths. In all dogs, the uroliths were composed of pure cystine. Twenty-six different breeds were recognized, including Dachshunds (34%), Tibetan Spaniels (10%), Basset Hounds (7%), Irish Terriers (5%), Rottweilers (5%), English Bulldogs (5%), French Bulldogs (5%), Shetland Sheepdogs (3%), Drevers (3%), Labrador Retrievers (3%), Scottish Deerhounds (2%), Yorkshire Terriers (2%), Welsh Corgis (2%), and Whippets (2%). Other breeds included Cavalier King Charles Spaniel, Munsterländer, Beagle, Chihuahua, Staffordshire Bull Terrier, Shih Tzu, Swedish Lapphund, Pekingese, Cairn Terrier, Silky Terrier, Vorster, and Basenji.

Before the start of tiopronin treatment, routine urinalysis urine culture, CBC, serum biochemistry analyses, and cyanide nitroprusside reaction tests were performed on each dog. All urine samples were collected in the morning before food was given, and the diet in all dogs was a mixture of commercial food and scraps from the household. Ultrasonography, or in a few dogs radiography, of the urinary tract was performed to detect recurrent uroliths. In dogs with recurrent uroliths, reexamination was done every 4th week until urolith dissolution occurred, or if dissolution did not occur, surgery was performed. Dogs without uroliths were reexamined between 2 and 4 times a year. Tiopronin was given in divided doses twice a day. Dogs without uroliths were given a daily dosage of 30 mg/kg body weight, and dogs with uroliths, a daily dosage of 40 mg/kg body weight. Besides tiopronin treatment, in the beginning of the study, the 1st 5 dogs were given sodium bicarbonate for urine alkalinization. The owners of the dogs were instructed to use test strips for monitoring the urinary pH of the dogs and to adjust the dosages of sodium bicarbonate to keep the pH over 7. However, because control measurements during 2 years disclosed that the urinary pH was between 5 and 6.5, we concluded that this prophylactic treatment was insufficient, and this regimen therefore was abandoned.

Before treatment, in 32 of 88 dogs, a quantitative measurement of the urinary excretion of cystine and the dibasic amino acids lysine, arginine, and ornithine was performed. In 22 of the 32 dogs (dogs 1–22), a 24-hour urine sample was collected,[7] and in 10 dogs (dogs 23–32), where 24-hour urine collection was impossible, the mean of 3 morning samples of urine was used. Dogs were fasted for 12 hours before urine samples were collected, and the urinary concentration of amino acids in each urine sample from all dogs was related to the urinary creatinine concentration, a method used by other investigators when 24-hour urine was not available.[34] In an earlier study, the reliability of the cystine:creatinine ratio, compared with the total 24-hour cystine excretion, was investigated.[7] The 2 methods were compared by linear regression analysis, and a strong positive correlation ($r = .97$, $P < .001$) was found between the methods.

Laboratory Tests

Urinary cystine and dibasic amino acids were measured by ion exchange chromatography with an LKB 4151 Alpha Plus amino acid analyzer.[2] The chromatograms were automatically evaluated by a Shimadzu C-R4A integrator at the Department of Clinical Chemistry, University Hospital in Malmö. No preservatives were added to the urine specimens, which were sent to the laboratory frozen (−20°C). Uroliths were analyzed at the Department of Chemistry, National Veterinary Institute in Uppsala, by infrared spectrophotometry with the KBr-disk technique, a well-documented semiquantitative method for the analysis of organic uroliths.[35,36]

Plaine radiography and retrograde pneumo cystography were performed. For ultrasound, a 7.5-MHz linear transducer[b] and a multihertz 7.5-MHz annular array sector transducer[c] were used.

Statistical Analysis

The correlation between urinary excretion of cystine and the dibasic amino acids was evaluated in 10 dogs (dogs 23–32), and the correlation between urinary excretion of cystine and age was evaluated in 32 dogs (dogs 1–32). The method used was 1-way analysis of variance and linear regression.[37,d] Students's *t*-test for unpaired data (logarithmic transformation of data) was used for differences in cystine excretion between dogs (dogs 1–32) with 1 or more episodes of cystine urolith formation.

Results

The mean age of the 88 dogs at the time of cystine urolith retrieval was 5.6 years (range, 1–12 years). Eleven percent of the dogs in the study were 2 years or less, and 13% were 9 years or older (Fig 1). Treatment time with tiopronin ranged from 1 month to 13 years (mean, 2.8 years). Fifty-two percent of the dogs were treated with tiopronin for 1 year or less and 22% for 5 years or more (Fig 2).

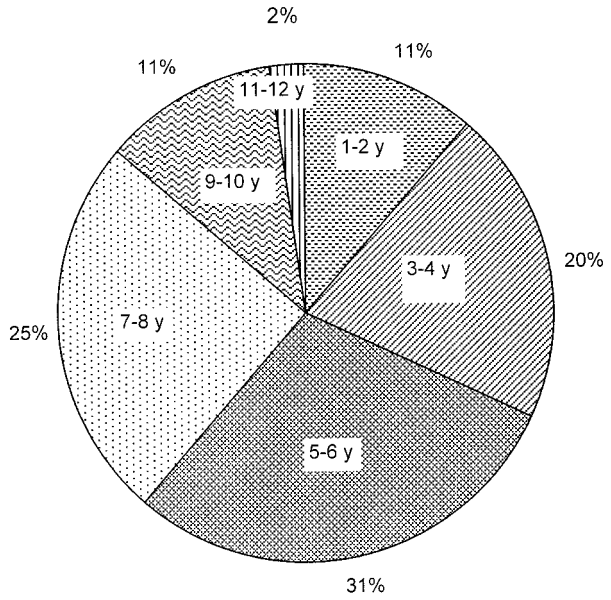

Fig. 1. Age distribution for 88 cystinuric dogs at time of cystine urolith retrieval.

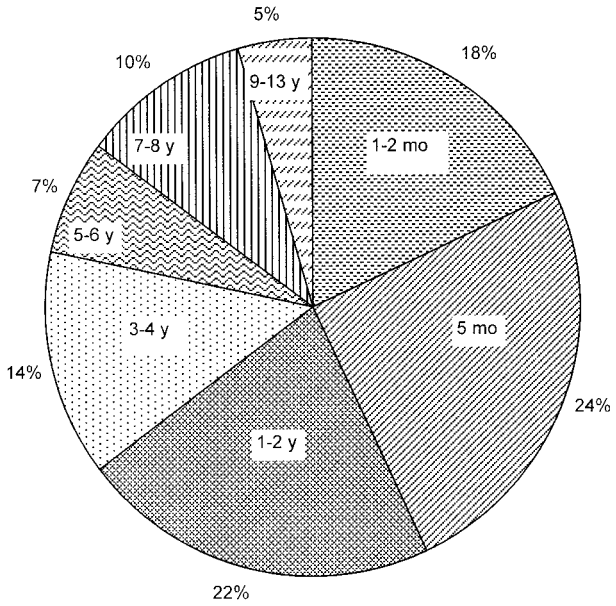

Fig. 2. Time distribution for treatment with tiopronin in 88 cystinuric dogs.

In 9 dogs, tiopronin treatment was stopped because of low cystine excretion (<15 mmol/mol creatinine) at a mean age of 9.1 years (range, 6–16 years). According to results from investigation of the urinary tract with ultrasound or radiography, no recurrence of uroliths was found in any of the dogs from 1 to 7 years (mean, 2.6 years) after termination of treatment. In 4 of the 9 dogs, a postmortem examination was performed, which confirmed the absence of calculi.

Thirty-five of the 50 dogs treated at the University Clinic in Uppsala were euthanized during the study. Mean age at euthanasia was 10.5 years (range, 2–18 years). The reason for euthanasia was a variety of diseases such as tumors in 6 dogs, chronic heart failure in 4 dogs, chronic urinary tract infection (UTI) in 3 dogs, chronic skin problems in 3 dogs, chronic renal failure in 3 dogs, chronic diarrhea in 2 dogs, acute pancreatitis in 2 dogs, diabetes mellitus in 2 dog, orchitis in 2 dogs, aggressiveness in 1 dog, and death occurred without known cause in 5 dogs. In 2 dogs, the reason for euthanasia was recurrence of uroliths.

The urinary excretion of cystine in 32 dogs at the start of the study varied widely between 2.0 and 295 mmol/mol creatinine. According to cystine excretion, the dogs could be divided into 3 groups. Six dogs showed low excretion with a mean of 9.5 mmol/mol creatinine (range, 2.0–18.2). Nineteen dogs showed a moderate excretion with a mean of 43 mmol/mol creatinine (range, 21.4–88.7), and 7 dogs showed high cystine excretion with a mean of 162 mmol/mol creatinine (range, 106–295). In 2 of the dogs, cystine excretion was within the range of the normal dogs (<10 mmol/mol creatinine).[2] However, on reevaluation within a period of 4 months, the urinary excretion of cystine ranged from 2.0 to 37.3 mmol/mol creatinine in 1 of the dogs and from 2.6 to 10.8 mmol/mol creatinine in the other dog.

The relationship between urinary excretion of cystine, lysine, ornithine, and arginine was evaluated by pairwise correlation in 10 dogs (dogs 1–10). Highly significant correlation ($P < .001$) with the excretion of cystine was found for lysine and ornithine, and a significant correlation ($P < .01$) was found with arginine. Also, among the dibasic amino acids, a highly significant correlation of excretion was found.

Figure 3 shows the relationship between urinary cystine excretion and age for the 32 cystinuric dogs. Older dogs (>5 years) were found to have significantly ($P = .0244$) lower cystine excretion than younger dogs (5 years or younger).

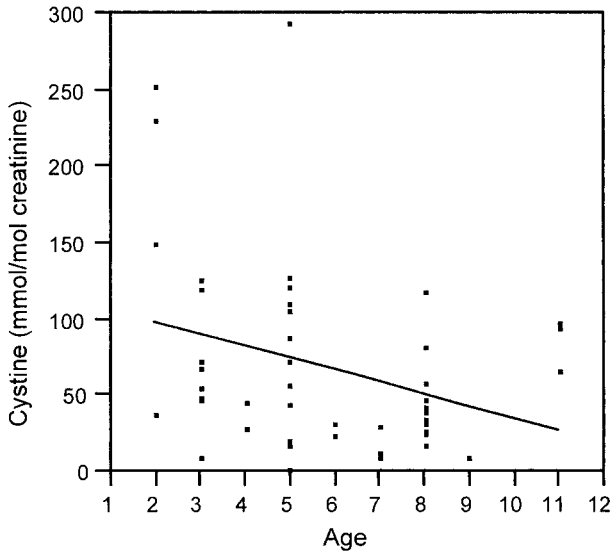

Fig. 3. Significant correlation ($P = .0244$) between urinary cystine excretion and age of 32 cystinuric dogs, evaluated by linear regression. Measurements were made before any medical treatment or change in diet was started.

Table 1. Adverse effects in 11 of 88 cystinuric dogs treated with tiopronin (Thiola®).

Breed	Dachshund, Scottish Deerhound, Rottweiler, Irish Terrier, Basset Hound, Tibetan Spaniel, Silky Terrier
Age of dogs (years)	Range 2–10 (mean 5.6)
Type of reaction	Proteinuria, thrombocytopenia, anemia, high liver enzyme activities and bile acids, tiredness, small pustules of the skin, aggressiveness, dry and crusty nose, sulfur odor of the urine, myopathy[a]
Duration of treatment (months)	Range 1–36 (mean 7.8)
Dose of tiopronin (mg/kg body weight)	Range 25–50 (mean 33.1)
Recovery time (weeks)	Range 1–16 (mean 4.2)

[a] Signs of myopathy included staggering and difficulty chewing and swallowing.

Sixteen out of 88 cystinuric dogs were found to have re-formed bladder stones at the start of tiopronin treatment, and in 10 of them (63%), the uroliths dissolved during treatment. Mean time for urolith dissolution was 1.6 months (range, 1–3 months). Later in the study, uroliths re-formed during tiopronin treatment in 12 dogs, and in 5 of them, the uroliths dissolved when the tiopronin dosage was increased from 30 mg/kg body weight to approximately 40 mg/kg body weight per day. Time to recurrence of cystine urolith formation varied between 1 and 36 months (mean, 7.9 months) before and between 3 and 36 months (mean, 18.2 months) during tiopronin treatment.

Two of the 12 dogs with uroliths that re-formed during tiopronin treatment were euthanized, and 5 of the 12 dogs were treated surgically. In 3 of the dogs with surgically removed uroliths, analysis of uroliths showed magnesium ammonium phosphate. Urine culture identified UTI with *Staphylococcus intermedius* in 2 of them. In the 3rd dog, urine culture was negative. All 3 dogs had been treated with sodium bicarbonate for 10–24 months. The urinary pH in the dogs at the time of urolith surgery was between 6 and 6.5. In 2 of the 3 dogs, urinary cystine excretion was measured at start of the study and at the time of surgery for struvite uroliths. In both dogs, cystine excretion was decreased, from 33.3 to 10.8 mmol/mol creatinine and from 48.1 to 2 mmol/mol creatinine, during a period of 10 and 18 months, respectively. None of the 3 dogs produced new uroliths after this episode.

Before the start of tiopronin treatment, urinary excretion of cystine for 19 dogs with a history of recurrent urolith formation varied between 18.2 and 295 mmol/mol creatinine (mean, 77.8). In 13 dogs with only 1 episode of urolith formation, cystine excretion varied between 2.0 and 121.9 mmol/mol creatinine (mean, 33.6). The difference in cystine excretion between the groups was statistically significant ($P = .0037$).

In 11 dogs, adverse reactions were recognized that could be related to tiopronin treatment (Table 1). The signs were noted between 1 and 36 months (mean, 7.6 months) after the start of treatment, and the most severe signs were aggressiveness and myopathy. According to the owners, 2 dogs became aggressive toward members of the families at 10–36 months, respectively, after start of treatment. In the 1st dog, the clinical signs disappeared when the tiopronin dosage was lowered. The 2nd dog, a 2-year-old Dachshund, showed signs of aggressiveness before the start of treatment, but according to the owner, the signs increased in severity during tiopronin therapy. On 3 occasions, the aggressiveness decreased when treatment was discontinued for 3–4 weeks, but as soon as treatment was started again, the temperament of the dog changed drastically. Eventually, the dog had to be euthanized. Autopsy, with macroscopic and microscopic examination of the brain, did not show any changes that could explain the behavior of the dog.

Signs of myopathy with bilateral masseter and quadriceps pain, weakness, staggering, and difficulty chewing and swallowing were detected in 2 unrelated Irish Terriers, 3–4 months, respectively, after start of treatment. One of the dogs had to be hospitalized for 6 days because of inability to swallow food and water, but during 4–8 weeks after termination of treatment, the clinical signs gradually disappeared. Proteinuria and thrombocytopenia were found in 3 and 4 dogs, respectively. The signs disappeared when treatment was stopped. Transient mild skin lesions were detected in 2 dogs. One dog developed small pustules on the abdomen, and the other dog developed a dry and crusty nose. The lesions disappeared when the dosage of tiopronin was lowered. An unpleasant sulfur odor of the urine was noted in 2 dogs. The odor disappeared when the tiopronin treatment was stopped.

Discussion

Fourteen years of clinical studies have shown the usefulness of tiopronin treatment of cystinuric dogs. Most dogs lived a normal life, and the mean age for 35 dogs euthanized during the period was 10.5 years. Apart from 2 dogs with re-formed uroliths and 5 dogs with unknown cause of death, the reason for euthanasia was not related to cystine urolith formation or tiopronin treatment. The occurrence of urolithiasis was reduced during tiopronin treatment. This finding was illustrated by the change in mean recurrence rate of uroliths from 7 months before to 18 months during tiopronin treatment. For prophylactic use, tiopronin was given PO at a daily dosage of approximately 30 mg/kg body weight. Based on earlier pharmacological studies of tiopronin in dogs, where rapid renal excretion was shown initially after administration of the drug, divided doses were recommended rather than 1 dose per day.[38] This study also shows the usefulness of tiopronin in cystine urolith dissolution. On 28 occasions, bladder stones were found, and in about 60% of the dogs, the uroliths dissolved.

Three dogs formed struvite uroliths during tiopronin and sodium bicarbonate treatment. Two of them had UTIs caused by *S intermedius.* Formation of struvite uroliths is favored by urease-producing bacteria in an alkaline environment.[39] However, the urinary pH in both dogs with UTI was approximately 6.0, so it remains unclear whether the formation of struvite uroliths and the lowered cystine excretion in these dogs depended on tiopronin treatment, as such, or reflected the aging of the dogs or some other unknown factor.

Most dogs treated with tiopronin tolerated the drug well. Adverse effects related to treatment were found in 11 dogs, however, and must be considered. Most of the adverse effects in humans related to tiopronin treatment are characterized by immunologic disturbances, as reviewed by Jaffe in 1986.[40] Proteinuria is the most commonly described manifestation, sometimes leading to membranous glomerulonephritis induced by immune-mediated reactions.[41] In this study, transient mild to moderate proteinuria was noted in 3 dogs, but in none of the dogs were further clinical signs of renal injury noted. Myopathy, which was found in 2 dogs, was a more severe adverse reaction. A similar reaction was reported in a cystinuric woman who developed transient bilateral quadriceps pain and weakness 7 days after the start of tiopronin treatment.[42] Another adverse effect was aggressiveness. This type of reaction because of tiopronin treatment has not been reported previously. All adverse effects caused by tiopronin disappeared when treatment was stopped.

Another clinical observation was that the tendency for cystine urolith formation seemed to decrease with increasing age. This effect was particularly evident in 9 dogs ending their tiopronin treatment at a mean age of approximately 9 years. Despite no further treatment, the dogs did not develop new uroliths during the remainder of their lives, possibly because of decreasing cystine excretion with increasing age, as shown in this study.

Results from this investigation show a significant correlation between excretion of cystine and that of the dibasic amino acids. This finding is in accordance with one of our earlier studies, indicating a shared transport mechanism in the renal tubules for cystine and the dibasic amino acids.[2]

Over the years, we have found extreme variability in urinary excretion of cystine with considerable overlap between clinically normal and cystinuric dogs, and urolith-forming dogs may have cystine excretion within the range of control dogs.[7] This finding also was described by Holtzapple et al in 1971[11] and suggests that high urinary cystine excretion is not the only factor to consider as the cause of cystine urolith formation. For the practitioner in the clinical situation, the cyanide nitroprusside reaction is a simple and useful method for the differentiation of normal and increased urinary cystine excretion. However, when uncertain, it is important to repeat the test, because some cystinuric dogs, on random urine sampling, may have a negative cyanide nitroprusside reaction (<10 mmol/mol creatinine) due to daily variations in urinary cystine excretion.

Individual variation in urinary cystine excretion makes it difficult to estimate a concentration above which cystine uroliths are likely to form. Results from this study, however, show that most frequently, there is markedly higher excretion of cystine in dogs with recurrent urolith formation compared to dogs with only 1 episode of urolithiasis. In human beings, at least 3 cystinuric groups have been recognized, based on the urinary concentration of cystine in obligate heterozytes.[14,43] Different subtypes of the tubular defect also probably exist in cystinuric dogs, resulting in varying degrees of cystine excretion. Newfoundland dogs with high urinary excretion of cystine, for instance, were described with severe impairment of tubular reabsorption.[20]

In conclusion, cystinuria causes a lifelong tendency for urolith formation, which, in some dogs with high urolith recurrence rate, may lead to euthanasia early in life. An individual strategy for treatment is therefore of the greatest importance (Table 2).

Table 2. Recommended scheme for treatment of cystinuric dogs.

Prophylactic treatment
Tiopronin[a] 30 mg/kg body weight (bw) q12, PO.
Increase water intake and urine diuresis.
Urine alkalinization (pH 6.5–7.0) using potassium citrate.
In cases with low cystine excretion and low urolith recurrence rate, tiopronin dose may be individually decreased (<30 mg/kg bw) or ended.
Dissolution of uroliths
Tiopronin approximately 40 mg/kg bw q12, PO.
Reevaluation of uroliths with ultrasound or radiography every 4th week.
After urolith dissolution, give prophylactic dose of tiopronin.
If urolith dissolution is not achieved after 2–3 months, surgery is recommended.
Reexaminations
Is recommended 1, 3, 6, and 12 months after start of treatment and thereafter twice a year, including:
Physical examination.
Ultrasonography/radiography of the urinary tract.
Urinalyses (specific gravity, protein, pH, sediment, and cyanide nitroprusside reaction) using morning samples of urine.
Blood analyses (hemoglobin, white blood cell count, thrombocytes, alkaline phosphatase, and alanine aminotransferase).
Quantitative measurements of urinary cystine excretion related to the urinary creatinine excretion, may be performed on morning samples of urine, before start of treatment and once a year during treatment.
If adverse reactions occur[b]
Stop treatment with tiopronin for 4 weeks.
Blood and urine analysis every week to every 2nd week until remission of signs.
When the adverse reactions have dissappeared, start tiopronin treatment again, gradually increasing the dose from 10 to 15 mg/kg bw q12.
If the adverse reactions reappear despite a lowered dose, tiopronin treatment has to be abandoned.

[a] Thiola®, tbl, 250 mg, Santen Pharmaceutical Co, Osaka, Japan.
[b] Adverse reactions to tiopronin may include thrombocytopenia, anemia, high liver enzyme activities, proteinuria, sulfur odor of the urine, dry and crusty nose, myopathy, and aggressiveness.

A wide range of urinary cystine excretion was found in the evaluated dogs, and there seemed to be a connection between the varied rates of cystine excretion and recurrence of cystine uroliths. Dogs with high cystine excretion had greater risk for re-formation of cystine uroliths compared to dogs with low cystine excretion. This finding may reflect different subtypes of the tubular disease resulting in varying degrees of cystine excretion. Occasionally, normal cystine excretion is found in urolith-forming dogs, which may reflect daily variation of urinary cystine excretion and may confuse the practitioner in the clinical setting.

The benefit of tiopronin treatment was shown by a decrease in urolith recurrence rate and urolith dissolution in dogs with re-formed uroliths.

Results of this investigation also show that urinary cystine excretion in some dogs decreases with increasing age. Consequently, the prophylactic tiopronin dosage should be decreased (<30 mg/kg body weight per day), and in some dogs, medication can be discontinued.

In the future, besides genetic studies for further identification of defective genes, a classification of cystinuria into different subtypes based on urinary phenotype will help in the differentiation of cystinuric dogs with high or low risk for cystine urolith formation.

Footnotes

[a] 2-mercaptopropionylglycine, Thiola®, 250 mg, Santen Pharmaceutical Company, Osaka, Japan
[b] Aloka SSD 650
[c] Interspec Rx 400
[d] SAS software, SAS Institute, Cary, NC

Acknowledgments

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