Povidone iodine sclerotherapy for treatment of idiopathic renal hematuria in two dogs

Lauren B. Adelman DVM
Joseph Bartges DVM, PhD
Jacqueline C. Whittemore DVM, PhD

From the Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, TN 37996. Dr. Bartges’ present address is Cornell University Veterinary Specialists, 880 Canal St, Stamford, CT 06902.

Address correspondence to Dr. Adelman (ladelman@utk.edu).

CASE DESCRIPTION
A 6-year-old spayed female Great Pyrenees (dog 1) and a 2-year-old spayed female German Shepherd Dog (dog 2) were evaluated because of gross hematuria of 5 and 2 months’ duration, respectively.

CLINICAL FINDINGS
In both dogs, coagulation times were within reference limits, results of aerobic bacterial culture of urine samples were negative, echogenic debris could be seen within the urinary bladder ultrasonographically, and hematuric urine could be seen exiting the right ureterovesicular junction, with grossly normal urine exiting the left ureterovesicular junction, during cystoscopy. A diagnosis of idiopathic renal hematuria was made in both dogs.

TREATMENT AND OUTCOME
Both dogs underwent retrograde ureteropyelography, unilateral povidone iodine sclerotherapy, and ureteral stent placement. The right ureter was occluded with a ureteropelvic junction balloon catheter, and a 5% povidone iodine solution was infused into the renal pelvis 3 times. A double-pigtail ureteral stent was then placed. Both dogs recovered without complications, with cessation of gross hematuria within 12 hours. Cystoscopic removal of the ureteral stent was performed in dog 1 after 4 months; at that time, the urine sediment contained 5 to 10 RBCs/hpf. In dog 2, urine sediment contained 50 to 75 RBCs/hpf 2 weeks after sclerotherapy, with continued resolution of gross hematuria 8 weeks after sclerotherapy. The owners declined removal of the stent in dog 2.

CLINICAL RELEVANCE
Findings suggested that povidone iodine sclerotherapy may be an effective renal-sparing treatment for idiopathic renal hematuria in dogs. Further evaluation with longer follow-up times is warranted. (J Am Vet Med Assoc 2017;250:205–210)

ABBREVIATIONS
IRH Idiopathic renal hematuria
UPJ Uretopelvic junction
UVJ Ureterovesicular junction

A 6-year-old 62.7-kg (137.9-lb) spayed female Great Pyrenees (dog 1) was referred to the University of Tennessee Veterinary Medical Center for evaluation and treatment of gross hematuria of 5 months’ duration. The dog had initially been brought to the referring veterinarian because of pollakiuria, stranguria, and hematuria. Urinary tract infection was diagnosed on the basis of results of a urinalysis, which revealed pyuria, hematuria, and the presence of rod-shaped bacteria. The dog was treated with trimethoprim-sulfonamide (16 mg/kg [7.3 mg/lb], PO, q 12 h) and carprofen (1.6 mg/kg [0.73 mg/lb], PO, q 12 h) for 20 days. The pollakiuria and stranguria resolved with this treatment, but intermittent gross hematuria persisted. One month after the initial examination, the dog was returned for further evaluation of the intermittent gross hematuria. Results of a CBC and serum biochemical profile were unremarkable, and the prothrombin time (6.5 seconds; reference interval, 5.5 to 12 seconds) and partial prothrombin time (10.8 seconds; reference interval, 10 to 25 seconds) were within reference limits. The dog was treated with doxycycline (4.8 mg/kg [2.2 mg/lb], PO, q 12 h) for 21 days; however, intermittent gross hematuria without other clinical signs of lower urinary tract disease persisted for the next several months, and aerobic bacterial culture of a urine sample did not yield any growth.

The only remarkable abnormalities on initial physical examination at the Veterinary Medical Center were a hooded vulva, vulvovaginitis, and obesity (body condition score of 8 on a scale from 1 to 9). Blood pressure was not measured. Urine obtained by means of ultrasound-guided cystocentesis was dark yellow and cloudy with a specific gravity of 1.025. Microscopic examination of the urine sediment revealed RBCs too numerous to count. No abnormalities were seen on abdominal radiographs. During abdominal ultrasonography, echogenic debris was seen within the urinary bladder; a single left renal cortical cyst that was believed to be an incidental finding was also identified.

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The following day, cystoscopy was performed with the dog under general anesthesia. The dog was premedicated with hydromorphone (0.1 mg/kg [0.045 mg/lb], IM), and anesthesia was induced with ketamine (5 mg/kg [2.3 mg/lb], IV), midazolam (0.5 mg/kg [0.23 mg/lb], IV), and propofol (2 mg/kg [0.9 mg/lb], IV) and maintained with inhaled isoflurane. A 2.7-mm, 30° angle, 18-cm-long rigid cystoscope was used to evaluate the vagina, vestibule, urethra, bladder, and right and left UVJs. There was mild vulvovaginitis, but otherwise, the vagina, vestibule, and urethra were grossly unremarkable. The urinary bladder contained urine with a dependent layer of blood as well as small blood clots. The left UVJ appeared normal, and grossly normal urine was seen exiting the junction. The right UVJ also appeared grossly normal, but grossly hematuric urine was seen exiting the junction (Figure 1). A biopsy specimen was obtained from the bladder wall for histologic examination and aerobic and anaerobic bacterial culture to rule out concurrent persistent cystitis. However, results of histologic examination of H&E-stained sections of the bladder wall were unremarkable, and bacterial culture did not yield any growth. A presumptive diagnosis of IRH was made on the basis of cystoscopic localization of hematuria to the right kidney or ureter without any identifiable cause for the bleeding. The dog was discharged pending purchase of supplies needed to perform sclerotherapy. Because of the vulvovaginitis, cephalexin (32 mg/kg [14.5 mg/lb], PO, q 12 h, for 14 days) was prescribed, and the owner was instructed to clean the area with 1% ketoconazole–2% chlorhexidine–2% acetic acid wipes twice a day for the next 7 days and apply a gentamicin sulfate–mometasone furoate monohydrate–clotrimazole otic suspension after cleaning.

Figure 1—Cystoscopic image of a 6-year-old Great Pyrenees examined because of hematuria of 5 months’ duration. Notice the grossly hematuric urine (asterisk) flowing from the right UVJ (black arrow). The left UVJ (white arrow) is also visible.

Twelve days later, the dog was returned to undergo sclerotherapy for treatment of the IRH. On physical examination, the vulvovaginitis had resolved, and no other abnormalities were noted. The dog was premedicated with hydromorphone (0.08 mg/kg [0.036 mg/lb], IM) and dexametomidine (2.9 µg/kg [1.3 µg/lb], IM). Anesthesia was induced with ketamine (4.1 mg/kg [1.9 mg/lb], IV), midazolam (0.4 mg/kg [0.18 mg/lb], IV), and propofol (2 mg/kg, IV) and maintained with inhaled isoflurane. Cefazolin (20 mg/kg [9 mg/lb], IV, q 4 h) was administered prophylactically.

Sclerotherapy was performed as previously described, with slight modifications. Once anesthetized, the dog was positioned in dorsal recumbency, and the vulva and perineal region were aseptically cleaned, after which the vulva was flushed with diluted chlorhexidine solution. Rigid cystoscopy was performed, and the bladder and right and left UVJs were examined. The bladder and left UVJ appeared grossly normal, but no urine was seen exiting from the right UVJ despite continuous observation for 5 minutes. Subsequently, a large blood clot exited the right UVJ, after which grossly hematuric urine was seen flowing from the right UVJ. At this time, the fluid used for irrigation was changed from saline (0.9% NaCl) solution to 5% dextrose in water to prevent RBC hemolysis and improve visualization.

Under cystoscopic and fluoroscopic guidance, a 0.035-inch, angle-tipped guidewire was advanced into the right UVJ and up the right ureter. A 5F open-ended ureteral catheter was then advanced over the guidewire with fluoroscopic guidance. The guidewire was removed, and retrograde ureteropyelography was performed with 76% meglumine diatrizoate. No gross lesions were identified. The distance from the right UVJ to the renal pelvis was determined to be 18 cm on the basis of fluoroscopic measurements.

The guidewire was reinserted and advanced into the right renal pelvis, and the ureteral catheter was then advanced to the level of the UPJ. The guidewire was removed and replaced by a stiff J-tipped wire to the level of the UPJ. Then, the ureteral catheter was removed, and a UPJ balloon catheter was advanced over the J-tipped wire to the level of the UPJ. The J-tipped wire and cystoscope were then removed. The balloon on the UPJ catheter was inflated with air to occlude the proximal end of the ureter. Contrast solution (76% meglumine diatrizoate diluted with an equal volume of 5% dextrose in water) was injected through the catheter under fluoroscopic guidance (Figure 2) to determine the renal pelvis filling volume (ie, the volume needed to fill the renal pelvis and calices without backfilling), which was 3 mL. The contrast solution was allowed to passively drain from the renal pelvis through the UPJ catheter.

Three times, the renal pelvis was infused with 3 mL of a 1:1:3 solution of 5% povidone iodine, 76% meglumine diatrizoate, and 5% dextrose in water. Each time, the povidone iodine solution was allowed to remain in place for 20 minutes and was then al-
PO, q 8 to 12 h, as needed), and carprofen (2.5 mg/kg q 12 h, for 7 days), tramadol (3.3 mg/kg [1.5 mg/lb], PO, q 12 h, for 5 days) were prescribed. The following morning, the dog was bright and alert, with no evidence of pain or discomfort. The dog urinated without stranguria, pollakiuria, or gross hematuria, after which it was discharged to the owners.

The dog was reevaluated at the Veterinary Medical Center 14 days after undergoing sclerotherapy. The owners reported that there had been no evidence of gross hematuria or other abnormalities since the time of discharge. Analysis of a urine sample collected by means of cystocentesis revealed a specific gravity of 1.006, but results were otherwise unremarkable. The urine sediment contained 0 to 2 RBCs/hpf (reference interval, 0 to 5 RBCs/hpf). On abdominal radiographs, the proximal end of the stent was seen to have migrated out of the renal pelvis and into the right ureter caudal to the kidney; however, there was no evidence of the stent in the urinary bladder on radiographs or ultrasonographic images, nor was there any evidence of right ureteral or renal pelvic dilatation. Because the dog was doing well clinically and was seemingly unaffected by the stent, a decision was made to leave the stent in place.

The dog returned to the Veterinary Medical Center 4 months later for a recheck examination. The owners reported that there had been no gross hematuria or other abnormalities since the time of discharge. A urine sample collected by means of cystocentesis was yellow and clear with a specific gravity of 1.015. The urine sediment contained 5 to 10 RBCs/hpf and rare transitional epithelial cells. Abdominal radiography and ultrasonography of the urinary tract revealed that the terminal end of the ureteral stent was located within the urinary bladder. The dog was premedicated with butorphanol (0.3 mg/kg [0.14 mg/lb], IV) and dexmedetomidine (2 µg/kg, IV), and anesthesia was induced with ketamine (2 mg/kg [0.14 mg/lb], IV) and propofol (6 mg/kg [2.7 mg/lb], IV) and maintained with inhaled isoflurane. The stent was removed cystoscopically with a snare device. No complications were encountered, and the dog was discharged the same day. At last follow-up 40 days after stent removal, the dog was reportedly clinically normal without recurrence of gross hematuria.

A 2-year-old 30.7-kg (67.5-lb) spayed female German Shepherd Dog (dog 2) was referred to the University of Tennessee Veterinary Medical Center for evaluation and treatment of gross hematuria of 2 months’ duration. The dog had been examined by the referring veterinarian 2 months earlier because of intermittent dark-red urine with no other clinical abnormalities. Results of a CBC and serum biochemical profile performed at that time were unremarkable. Examination of a free-catch urine sample revealed RBCs and WBCs, and the dog was prescribed amoxicillin (16 mg/kg, PO, q 12 h for 10 days). Ten days later, the dog was returned to the referring veterinarian because of progressive gross hematuria and lethargy. The prothrombin time (17.5 seconds; reference interval, 14 to 19 seconds) and partial prothrombin time were within reference limits, and abdominal radiographs were unremarkable. Aerobic culture of a
The dog recovered from anesthesia without any complications and was hospitalized in the intensive care unit overnight for monitoring. Crystalloid fluids were administered at a maintenance rate (60 mL/kg/h, IV). Amoxicillin (20 mg/kg, PO, q 12 h, for 10 days), tramadol (3.3 mg/kg, PO, q 12 h, as needed), trazadone (1.6 mg/kg, PO, q 12 h, as needed), and carprofen (1.6 mg/kg, PO, q 12 h, for 3 days) were prescribed. The following morning, the dog was bright and alert, with no evidence of pain or discomfort. The dog urinated without stranguria, pollakiuria, or gross hematuria and was discharged to its owners.

The dog was reevaluated by its primary care veterinarian 14 days after undergoing sclerotherapy. The owners reported that there had been no evidence of gross hematuria or other abnormalities since the time of discharge. Results of a CBC and serum biochemical profile (including measurement of serum electrolyte concentrations) were unremarkable. A urine sample obtained by means of cystocentesis was yellow with 50 to 75 RBCs/hpf in the urine sediment. Aerobic bacterial culture of the urine sample did not yield any growth. There were no apparent complications associated with the ureteral stent, and the owners declined removal. Approximately 2 months after the dog underwent sclerotherapy, the owners reported that they had not seen any evidence of gross hematuria.

Discussion

Findings for the 2 dogs in the present report suggested that povidone iodine sclerotherapy may be an effective renal-sparing treatment for IRH in dogs. However, additional study with longer follow-up times is needed to determine the overall success rate associated with this technique and to determine whether the condition will recur following treatment.

Idiopathic renal hematuria refers to gross hematuria originating from the upper urinary tract in the absence of an underlying cause of bleeding. The diagnosis is made by ruling out potential underlying causes of hematuria, such as calculi, infection, neoplasia, and coagulopathy. Idiopathic renal hematuria is rare in people and appears to be uncommon in veterinary patients. The condition typically occurs in large-breed dogs that are young, often < 2 years old, and otherwise healthy, and there is no obvious sex predilection. The condition is reported to occur bilaterally, either at the time of diagnosis or as a progression from unilateral disease, in > 20% of affected dogs. The underlying abnormality has not been definitively elucidated in dogs. In people, IRH is a result of renal pelvic vascular abnormalities resulting in spontaneous hemorrhage, and a similar mechanism is proposed in dogs. Although IRH may follow a benign course for extended periods, anemia or iron deficiency secondary to chronic blood loss and urethral or ureteral obstruction with blood clots can occur. Because these complications can be life-threatening, treatment is usually recommended. Historically, ureteronephrectomy was used to treat IRH in dogs. However, because many dogs have or will develop bilateral involvement and because lesions typically occur in the renal pelvis rather than the renal parenchyma, ureteronephrectomy is no longer recommended.

Recently, novel treatment options for IRH modified from the human literature have been explored.
in dogs.\textsuperscript{1,16} Specifically, sclerotherapy is a procedure that involves injection of a chemical irritant into the renal pelvis to cause sclerosis of the vasculature. It can be performed with silver nitrate, povidone iodine, or both agents in series. Silver nitrate is a coagulating and chemical cauterring agent that has been used for the treatment of IRH and chyluria in people.\textsuperscript{7,18} In human patients undergoing silver nitrate sclerotherapy for treatment of IRH, flank pain, nausea, and vomiting are common adverse effects.\textsuperscript{18} Rarely, more serious complications have been reported, including acute necrotizing ureteritis, stricture formation, chemical cystitis, bladder wall fibrosis, arterial hemorrhage, and hepatic and renal failure.\textsuperscript{19–22} Other disadvantages of using silver nitrate for sclerotherapy include difficulties in procuring high-quality product and precisely weighing it and silver nitrate’s water insolubility and its susceptibility to decomposition when exposed to light.\textsuperscript{18} The need to prepare fresh solutions for each patient can also result in a delay in treatment.\textsuperscript{18}

Povidone iodine is a corrosive and granulating agent that is believed to work synergistically with silver nitrate.\textsuperscript{1} Although there are fewer reports of the use of povidone iodine as a sole sclerotherapeutic agent in human medicine, adverse effects have not been reported,\textsuperscript{18} which could make it a safer choice in veterinary patients. Additionally, povidone iodine is readily available and easy to reconstitute, and quality control is easier to ensure.\textsuperscript{23} Povidone iodine has been used as a sclerosing agent to successfully treat human patients with chyluria associated with malaria-like disease,\textsuperscript{17,23–26} and in 1 study,\textsuperscript{23} there was no significant difference in outcome between people receiving 1% silver nitrate sclerotherapy and those receiving 0.2% povidone iodine sclerotherapy for the treatment of chyluria. The combined use of silver nitrate and povidone iodine has not been investigated, to the authors’ knowledge, for treatment of IRH in people. To the authors’ knowledge, there are also no published reports on the use of povidone iodine as a sole sclerotherapeutic agent for the treatment of IRH in people or dogs.

Two previous reports\textsuperscript{1,16} on the use of sclerotherapy for treatment of IRH in dogs have been published. One of these was a single case report\textsuperscript{16} that described resolution of clinical signs and anemia for 10 months following surgically assisted unilateral instillation of 0.5% silver nitrate in a dog with bilateral IRH. This dog was ultimately euthanized following recurrence of hemorrhage after nephrectomy. The other was a case series\textsuperscript{1} that described short- and long-term outcomes after endoscopic and fluoroscopic-guided sclerotherapy in 6 dogs with IRH. In these dogs, a 5% povidone iodine mixture was infused into the renal pelvis twice, followed by a 0.5% to 1.0% sterile silver nitrate solution 3 times. Long-term resolution of hematuria was documented in 4 of the 6 dogs (5/8 affected renal pelvises). All dogs in that series had > 50% improvement in gross hematuria, along with complete resolution of anemia, pollakiuria, and stranguria. Five of the 6 dogs recovered without complications; the remaining dog developed clinical signs of ureteritis following the procedure. Because this dog was the only dog that did not have a UPJ balloon used or a ureteral stent placed, we elected to recommend ureteral stent placement following sclerotherapy for the 2 dogs in the present report to minimize chemical irritation, which could lead to ureteritis or urethral spasm.

Silver nitrate was not available at the time dog 1 in the present report was treated. Because of concerns that ureteral obstruction would occur if treatment was delayed, povidone iodine was used as a sole sclerotherapeutic agent. On the basis of the successful outcome for dog 1, the same protocol was subsequently used in dog 2. Neither dog had any adverse treatment effects, and clinical signs resolved in both. To the authors’ knowledge, this was the first report of successful treatment of IRH in a dog or human with povidone iodine as a sole sclerotherapeutic agent.

Stent migration, which occurred in dog 1 of the present report, occurred in 3 dogs of the previous case series.\textsuperscript{1} One dog passed the stent during urination, 1 stent was removed cystoscopically, and the third stent was left in place owing to a lack of clinical signs and resolution of hematuria.\textsuperscript{1} Although stent migration occurred in dog 1, this was not unexpected given the inadequate length of the stent when placed. Cystoscopic removal was not performed because, at the time of the initial procedure, a longer stent was not available with which to replace the shorter stent. Because the patient was showing no clinical signs associated with stent migration, retrieval was not attempted at the time of the first recheck examination. When the dog was examined 4 months later, however, the stent had migrated into the urinary bladder and was cystoscopically removed, as has been previously recommended.\textsuperscript{1} No complications have been reported since the removal. In dog 2, no complications associated with the ureteral stent were reported, and the stent was still in place 2 months after sclerotherapy.

Acknowledgments

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Footnotes

\begin{itemize}
\item a. Karl Storz Endoscopy-America Inc, Culver City, Calif.
\item b. Weasel Wire hydrophilic guide wire, Infiniti Medical, Menlo Park, Calif.
\item c. Cook Medical, Bloomington, Ill.
\item d. MD 76R, USP, Mallinckrodt Pharmaceuticals, St Louis, Mo.
\item e. Amplatz Super Stiff guidewire (0.025 in. 145 cm), Boston Scientific, Natick, Mass.
\item f. UPJ occlusion balloon catheter (5.3F, 75 cm), Cook Medical, Bloomington, Ill.
\item g. Vet-Stent Ureter, Infiniti Medical LLC, Menlo Park, Calif.
\item h. Universal Firm Ureteral Stent and Positioner, Cook Medical, Bloomington, Ill.
\end{itemize}

References

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From this month’s AJVR

Pharmacokinetics of terbinafine in little brown myotis (Myotis lucifugus) infected with Pseudogymnoascus destructans

Michael H. Court et al

OBJECTIVE
To determine the pharmacokinetics of terbinafine in little brown myotis (Myotis lucifugus) infected with Pseudogymnoascus destructans.

ANIMALS
123 bats from a P destructans–infected hibernation site in Virginia.

PROCEDURES
3 bats were euthanized and necropsied to confirm the presence of P destructans within the population. The remaining 120 bats were systematically assigned to 6 groups (20 bats/group). Bats in each of 3 groups received 6, 20, or 60 mg of terbinafine/kg, SC, once daily for 10 days. Bats in another group received 200 mg of terbinafine/kg, SC, once daily for 5 days. Bats in a group received the terbinafine vehicle solution (0.1 mL/kg, SC, once daily for 10 days). Bats in the remaining group did not receive any treatment. (Following the treatment period [days 1 through 10]), bats were housed in a hibernation chamber and monitored daily until euthanasia on day 42, 75, or 109. Tissue specimens were collected from all bats as soon as possible after death or euthanasia to determine terbinafine concentration. Within each group and tissue type, terbinafine concentration data were pooled, and pharmacokinetic parameters were calculated by noncompartmental methods.

RESULTS
Adverse neurologic effects and a high mortality rate before day 10 were observed in bats that received the highest terbinafine dose (200 mg/kg) but not those that received lower doses. Presumed therapeutic terbinafine concentrations (≥2 μg/g) were maintained in skin and wing for at least 30 and 6 days in bats that received the 60 and 20 mg/kg doses, respectively, but were not achieved in most bats that received the 6 mg/kg dose. Tissue terminal half-life ranged from 14 to 22 days. Terbinafine concentration in hair was positively correlated with that in skin and wing.

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated terbinafine doses > 6 but < 200 mg/kg should be further evaluated for the treatment of P destructans–infected bats. Collection of serial hair specimens may represent a noninvasive method for monitoring terbinafine concentration in treated bats. (Am J Vet Res 2017;78:90–99)