USE OF ABSOLUTE ETHANOL FOR EMBOLIZATION PROCEDURES IN VETERINARY MEDICINE: A CLINICAL APPLICATION IN THE TREATMENT OF UNILATERAL ECTOPIC URETER IN THREE FEMALE DOGS

Absolute ethanol als embolisatiemiddel. Toepassing bij de behandeling van unilaterale ectopische ureters bij drie honden

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ABSTRACT

Absolute ethanol is a widely used embolization substance in human beings but has no definite indication in animals. In this study, three dogs with a unilateral ectopic ureter were treated by renal embolization with sterile absolute ethanol using a previously described technique. Immediate cessation of urinary incontinence was observed in two cases, while the third case improved but showed persistent urinary incontinence that was ascribed to vesicourethral sphincter incompetence. Post-interventional complications were the same as those encountered with the more conventional surgical techniques. Other possible applications of embolization procedures with absolute ethanol are briefly discussed.

Keywords: Kidney - Embolization - Dog - Ectopic ureter

SAMENVATTING

In de humane geneeskunde wordt pure ethanol frequent gebruikt als embolisatiemiddel maar in de diergeneeskunde kent deze techniek echter geen specifieke toepassing. In deze studie werden drie honden met een unilaterale ectopische ureter behandeld door middel van renale embolisatie. Hiervoor werd steriele pure ethanol gebruikt volgens een vroeger beschreven techniek. In twee gevallen stopte het urineverlies onmiddellijk. De urineïncontinentie verminderde, maar ging niet volledig over bij de derde hond. De persistente incontinentie in dit laatste geval was te wijten aan incompetentie van de vesicourethrale sfincter. Complicaties na de embolisatietechniek waren dezelfde als de verwikkelingen die men mag verwachten na meer conventionele chirurgische technieken. Andere mogelijke toepassingen van embolisatietechnieken met pure ethanol worden kort besproken.

INTRODUCTION

Absolute ethanol is a liquid embolization substance that has been successfully used in the treatment of many vascular diseases in human medicine (Novak, 1990). Major applications include infarction of renal tumors, renal ablation in patients with uncontrollable hypertension, obliteration of esophageal varices, bronchial artery embolization, transcatheter splenectomy, spermatic vein occlusion and treatment of arteriovenous malformations of the extremities (Novak, 1990).

Absolute ethanol has been proven to be the optimal embolization material for functional ablation on normal and pathologic kidneys, due to its cytotoxic (direct cellular toxicity) and angiotoxic (delayed arterial thrombus formation resulting in vascular occlusion) properties, and its low viscosity (Wallace *et al.*, 1981). Furthermore, ethanol is inexpensive, readily available, and easy to handle and maintain sterile compared with other embolization materials.

This report describes a clinical application of renal ethanol embolization in the management of unilateral ectopic ureter in three dogs after the owners decided against open surgery to reimplant the ureter. It also discusses other potential applications of embolization with absolute ethanol in veterinary medicine.

MATERIALS AND METHODS

Three female dogs were treated in this study: an 8-month-old Collie (dog 1), a 3-month-old Golden Retriever (dog 2) and a 4-month-old Rottweiler (dog 3). Respective weights were 20 kg, 14 kg and 20 kg. All dogs were presented with a history of continuous urinary incontinence since birth, with occasionally normal micturition. Physical examination, hematologic tests and biochemistry blood work were carried out on the three dogs. A urinalysis including physical examination, biochemical tests, urine sediment analysis, urine culture and evaluation of the renal function by the creatinine clearance test was also performed. The diagnostic imaging methods performed for each dog included: intravenous urography, abdominal ultrasonography (RT 6800, General Electric Medical Systems S.A., Belgium) and computed tomography (PQ 2000, Picker, USA). Urethral pressure profilometry was also obtained using a technique previously described by Rosin *et al.* (1980).

One week after diagnostic evaluation, transcatheter embolization of the affected kidney was performed. Preanesthetic medication with acepromazine (0.1 mg/kg body weight, IM) and methadone (0.4 mg/kg body weight, IM) was given. General anesthesia was induced with fentanyl (0.005 mg/kg body weight, IV) and propofol (2-8 mg/kg body weight, IV), and maintained with isoflurane and oxygen via a 'to-and-fro' semi-closed circuit. A Lactated Ringer's solution was supplied intravenously via a cephalic vein catheter at a rate of 10 ml/kg/h.

The right femoral artery was punctured with an 18-gauge needle using a modified Sedlinger technique, and a 5-French (F) hemostatic valve sheath (Check-Flo Introducers Set, William Cook Europe A/S, Denmark) was introduced. A midstream aortogram, with catheter tip placed 1 to 2 cm cranial to the celiac artery, was obtained via a 5-F pigtail catheter (Pigtail catheter, Royal Flush Plus, William Cook Europe A/S, Denmark) at an injection rate of 7 ml/sec for a total volume of 20 ml of contrast medium (Iohexol, Omnipaque 350, Nycomed, Norway) (Fig. 1a). A 5-F cobra catheter (Cobra catheter, William Cook Europe A/S, Denmark) was then passed into the renal artery using a 0.035 inch J-shaped guide wire (J wire guide, William Cook Europe S/A, Denmark). A digitally substracted renal angiography was performed by hand injection of 7 ml of iohexol (Fig. 2). A 3-F coaxial catheter system (Radifocus catheter, Terumo, Belgium), advanced through the cobra catheter, was used for selective catheterization of the interlobar renal arteries and renal tissue embolization (Fig. 3). Embolization was performed by repeated slow injections of 1-2 ml of sterile absolute ethanol into each interlobar branch. Contrast medium was injected by small volumes to control the progress of vaso-occlusion (Fig. 4). After removal of the catheter and the hemostatic valve sheath, digital pressure was applied on the puncture site to preserve the femoral artery. At the end of the procedure, a single injection of buprenorphine (0.01 mg/kg body weight, IV) was given to reduce pain related to renal ischemia. All three dogs were sent home one day after the procedure.

Two months after treatment, angiographic control of the renal vascularization was performed. Anesthesia, placement of the hemostatic valve sheath and a midstream aortogram were performed according to the previously described protocol. Two injections of 25 ml of non-ionic contrast medium were made at an injection rate of 8 ml/sec and with a time interval of 3 minutes. A fluoroscopic evaluation of the lower urinary tract was done following these injections.

Complete blood tests and urinalysis were obtained 2, 6, 9 and 12 months after the procedure. A computed tomographic examination was also performed after 6 months in two dogs. A follow-up of at least 2 years was obtained for each dog.

RESULTS

Pre-interventional and procedural results

Table 1 gives the results of pre-interventional laboratory data, urinalysis, urethral pressure profile, the site of ectopic ureter termination and associated abnormalities. The procedure time and volume of absolute ethanol are also indicated.

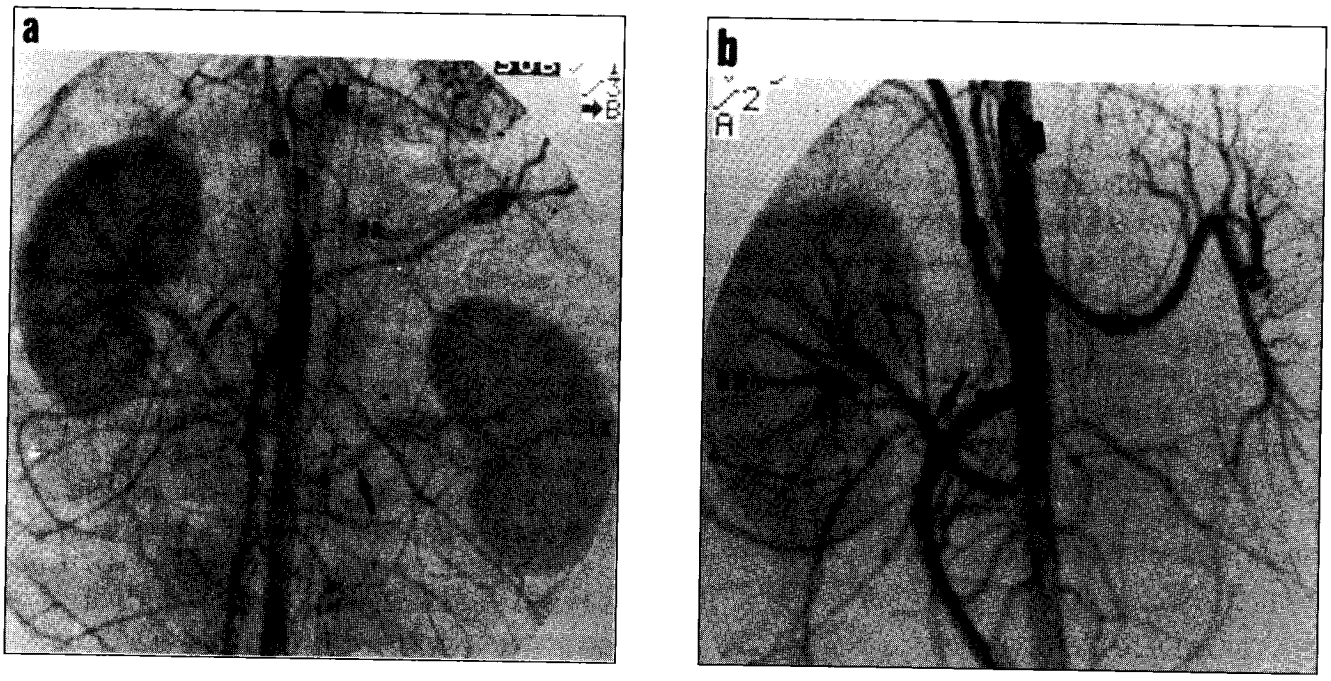

Figure 1. Dog 1 - a. Midstream abdominal aortogram, with catheter tip placed 2 cm cranial to the celiac artery, performed before embolization procedure. b. Midstream abdominal aortogram performed two months after embolization. The fact that the left renal artery and the parenchyma are not opacified indicates complete devascularization.
A = aorta; RK = right kidney; LK = left kidney; CMA = cranial mesenteric artery; HA = hepatic artery; SA = splenic artery; renal arteries (arrows); catheter tip (arrowhead).

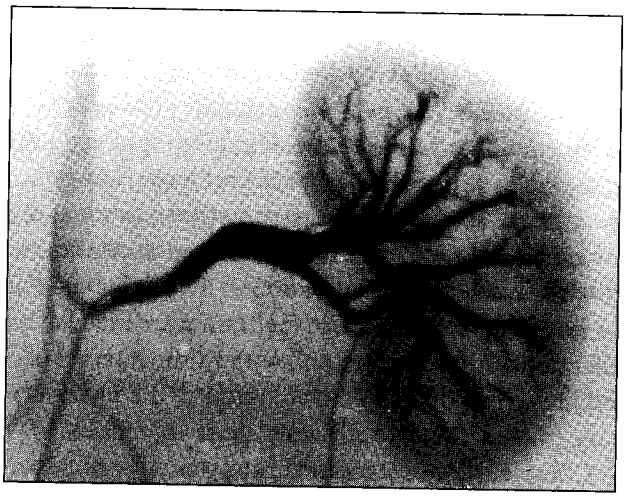

Figure 2. Selective renal angiography after placement of a cobra catheter into the left renal artery in dog 1.

Figure 3. Angiogram after selective catheterization of a small branch of the renal artery using a 3 Fr Radifocus catheter in dog 1. The left ureter is dilated. LK = left kidney; LU = left ureter.

None of the three dogs had an intrapelvic bladder neck position on plain radiographic examination or after intravenous urography.

Post-interventional results

Dog 1

Antibiotic therapy using Cefazolin (20 mg/kg body weight BID, PO) was given for 10 days. The owner observed elimination of necrotic debris and mild pain at micturition for 9 days.

Two months after embolization, the angiographic control demonstrated complete devascularisation of the renal parenchyma (Fig.1b). The dog presented a cystitis that was due to *Proteus mirabilis* and was treated with ampicillin (20 mg/kg body weight TID) for six weeks. The incontinence improved markedly for 5 months. At the nine-month follow-up, a recur-

Figure 4. Interstitial stasis of contrast medium, confirming complete vaso-occlusion in dog 1. The left ureter is dilated.

rent cystitis was again treated with ampicillin (20 mg/kg body weight TID) for six weeks. At 12 months, urinalysis revealed a pH of 8.0. Renal function tests performed at 2, 9 and 12 months were normal. A basic treatment with antibiotics was maintained to prevent further reinfection. Between the 12-month and the 36-month follow-up, the dog was clinically normal.

Dog 2

Antibiotic therapy using cefazolin (20 mg/kg body weight BID, PO) was given for 6 weeks because of pre-operative bacterial urinary tract infection. A discharge of necrotic debris lasted a few days, though it was not associated with pain on micturition. Incontinence disappeared within a few days.

The two-month angiographic control demonstrated complete devascularization of the embolized kidney. Computed tomographic examination obtained 6 months after embolization showed a compensatory

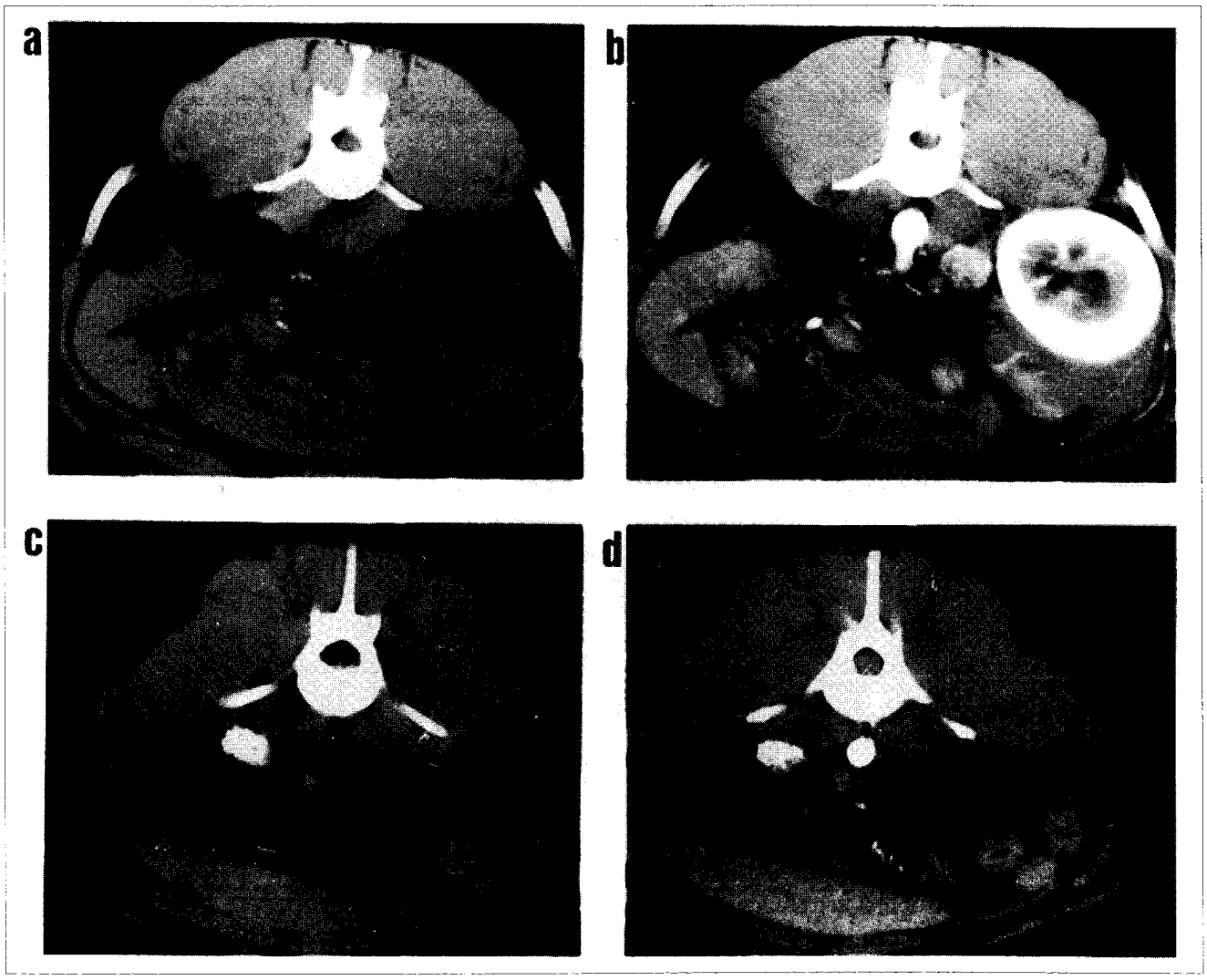

Figure 5. Tomographic examination of dog 3, obtained 6 months after embolization. A. Normal right kidney. B. Normal right kidney after iohexol contrast injection. C. Embolized left kidney (arrow), which is partly calcified and appears markedly diminished in size. D. The embolized left kidney (arrow) was not opacified after intravenous contrast injection.

Table 1. Results of pre-interventional examinations: laboratory data, urinalysis and urethral pressure profile, site of ectopic ureter termination and associated abnormalities. The procedure time and volume of absolute ethanol used for embolization are also indicated (UPP = urethral pressure profile).

Breed	Associated abnormalities	Laboratory data	Urinalysis	Ureter termination	UPP	Procedure time (min)	Volume of ethanol (mL)
1. Collie	Vaginal stricture	Normal	Normal	Caudal urethra	Normal	15	10
2. Golden Retriever	Ipsilateral hydroureter	Normal	Cystitis	Caudal urethra	Normal	20	12
3. Rottweiler	Ureteral diverticulum	Normal	Cystitis	Neck of the bladder	Decreased	15	11

hyperplasia of the left kidney that measured 9 cm in length, as compared to 7 cm on the first examination. The embolized right kidney, that had the same length as the left kidney on the first examination, measured 3 cm in length and was not opacified after intravenous contrast injection.

Complete blood tests, renal function test and urinalysis at 2, 6, 9 and 12 months were normal.

Dog 3

The procedure was partially successful as the dog showed improved clinical symptoms, though the urinary incontinence persisted.

The two-month angiographic control indicated complete left renal devascularization. Fluoroscopic evaluation of the lower urinary tract revealed the presence of a vesicoureteral reflux when the bladder was full. The 6-month-tomographic examination showed a calcified embolized kidney that measured 4 cm in diameter (as compared with 7 cm prior to embolization) and did not opacify after intravenous contrast medium injection (Fig 5). The right kidney had moderately increased in size. Blood tests performed at 2 and 6 months were normal. Treatment with phenylpropanolamine improved the incontinence. The dog died two years after the procedure for reasons unrelated to urinary tract pathology. Necropsy was performed and showed that the embolized kidney was small and calcified. Histology revealed an obliterated architecture with areas of coagulation necrosis, hemorrhage, calcification and lympho-plasmocytary inflammatory reactions.

DISCUSSION

Urinary incontinence due to anatomic anomalies cannot be treated by medical management. Various surgical techniques have been described for the treatment of ectopic ureter. The choice is determined by the unilateral or bilateral character of the anomaly, the type of ectopic ureter and the functional status of the kidneys (Owen, 1973; Stone and Mason, 1990; Rawlings, 1990). Ureteral reimplantation is chosen when the ectopic ureter is extramural (Stone and Mason, 1990; Rawlings, 1990). When the ureteral termination is intramural, an intracystic ureteric transplantation should be performed (Stone and Mason, 1990; Rawlings, 1990). The degree of ureteral dilation, which is used as a predictive factor for the success of surgical reimplantation as applied in human medicine, cannot be considered helpful in the dog (Rawlings, 1990). Complications resulting from the two techniques mentioned above include persistent urinary tract infections, hydronephrosis, transient or permanent stenosis of the distal ureteral orifice and calculus formation near the orifice of ureteroneocystotomy (Dean *et al.*, 1988 ; Stone *et al.*, 1990). Except for the urinary tract infections, all of these complications usually require surgical intervention, which greatly increases cost. Nevertheless, therapeutic techniques aimed at preserving renal function are to be preferred and should be utilized whenever possible. Ureteronephrectomy may be selected in cases where there is a unilateral ectopic ureter with an ipsilateral hydro-

nephrotic or infected kidney when the opposite kidney appears normal (Rawlings, 1990). The disadvantage of ureteronephrectomy is the loss of a kidney, with the consequent increased risk in cases of recurrent urinary tract infections, which are more frequently encountered in patients with ectopic ureter and (though to a lesser degree) in patients with renal tumors.

The advantages of embolization techniques as compared with surgery include the less invasive procedure, the shorter duration of anesthesia and the shorter hospitalization time. Furthermore, renal infarction provides a greater stimulus for contralateral compensatory hypertrophy as compared with renal ablation (Filippich *et al.*, 1984). The major disadvantages are the loss of a kidney and the need for a radiographic room with high quality fluoroscopy. Potential complications include incomplete tissue ablation, abscess formation and reflux of ethanol in systemic arteries. Incomplete infarction has been observed with particulate material but is unlikely to occur with ethanol, as this substance produces immediate cellular death at the injection target (Ellman *et al.*, 1980). Abscess formation is unlikely since no foreign particulate matter is injected and ethanol itself appears to discourage infectious reactions (Nanni *et al.*, 1983). However, abscess formation after renal ethanol embolization has been reported in humans (Rabe *et al.*, 1982). Reflux of ethanol in other arteries leading to tissue necrosis or nerve damage is unlikely at slow injection rates (Ellman *et al.*, 1980 ; Wallace *et al.*, 1981). Furthermore, direct injection of ethanol in the aorta of dogs showed no evidence of acute or delayed damage (Ellman *et al.*, 1980). Superselective catheterization of small renal branches decreases the risk of leakage of absolute ethanol into the aorta and other vessels but requires expensive catheters. Nevertheless, focal microscopic necrosis of the ipsilateral adrenal gland after renal ethanol embolization was observed in 5 out of 8 dogs in one study (Ellman *et al.*, 1980). This may be explained by the complex blood supply of the adrenal gland in the dog, which is provided by 20 to 30 arterioles arising from several major vessels, including the renal artery (Hullinger, 1993). This complication has no clinical impact and may be avoided by superselective catheterization into the interlobar renal arteries. In human patients, two cases of colonic infarction following ethanol embolization of renal cell carcinoma have been described (Cox *et al.*, 1982). Aortic reflux and streaming of ethanol in the inferior mesenteric artery was assumed to be responsible for this complication. In dogs, the caudal mesenteric artery has a caudal location, approximately 4 cm cranial to the termination of the aorta, by way of contrast to the human patients, where it is situated more closely to the renal arteries. All these complications may be avoided by proper technique. A postembolization syndrome, including variable degrees of pain and/or vomiting and slight fever for a period of one to five days, has been observed in human patients (Wallace *et al.*, 1981). Such a syndrome was not observed in this study.

In human medicine, the use of a balloon occlusion device has been described, which is utilized to decrease the total dose of ethanol necessary for complete ablation and to prevent potential reflux of ethanol (Thomson and Walters, 1993). We believe this is dangerous and unnecessary, as it gives a false impression of security. Furthermore, the preservation of the blood flow favors the peripheral distribution of ethanol and consequently limits the risk of unpredictable reflux of ethanol. The end point of the procedure is the appearance of interstitial parenchymal stasis of contrast medium during angiographic controls, indicating rupture of the capillary network, extravasation of contrast medium and coagulation of proteins, eliminating any further capillary perfusion of tissue.

Percutaneous chemical parathyroidectomy with ethanol (96%) has been performed in four dogs with parathyroid adenomas (Long *et al.*, 1998). The procedure resulted in rapid and complete normalization of calcium and parathyroid hormone (PTH) levels. No recurrence was observed during the 6-month follow-up period. Ultrasound-guided percutaneous injection has also been successfully performed for the treatment of eight dogs with primary hyperparathyroidism (Goldstein *et al.*, 1999a), four cats with unilateral hyperthyroidism (Goldstein *et al.*, 1999b) and six cats with bilateral hyperthyroidism (Wells *et al.*, 1999). Finally, embolization of hepatic or renal masses may be performed using an intra-arterial approach. The ablation of adrenal glands has been attempted in human beings, but appeared ineffective and risky (Novak, 1990).

The post-procedure complications observed in this study correspond to those observed after surgical correction of an ectopic ureter. Between 39.5 and 67 % of the treated animals may have some degree of persistent incontinence after surgical resection or reimplantation (Holt and Holston-Moore, 1995). In this study, two out of the three dogs had incontinence following treatment. In dog 1, two episodes of transient inconti-

nence were observed during the follow-up period; urinary bladder infection was assumed to be responsible for this condition. After these two episodes, basic antibiotic therapy was initiated to prevent further reinfection (Osborne and Feeney, 1995). Dog 3 had improved, incontinence after intervention. This was ascribed to the preoperatively demonstrated vesicourethral incompetence was confirmed by the cessation of the incontinence after administration of phenylpropanolamine. Vesicoureteral reflux increases the risk of ascending urinary tract infection, which otherwise is unlikely to occur (Osborne and Feeney, 1995).

To conclude, the present study has demonstrated the feasibility of the absolute ethanol technique for treating ectopic ureters in dogs. However, due to the small number of dogs used in this study and the lack of histopathologic examination in all dogs, further studies need to be performed on a larger number of dogs with normal and pathologic kidneys before recommending it over ureteronephrectomy.

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