Effects of an extract of *Serenoa repens* on dogs with hyperplasia of the prostate gland

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Objective—To determine effects of an extract of *Serenoa repens* on dogs with prostatic hyperplasia.

Animals—20 mature male dogs with benign prostatic hyperplasia.

Procedure—Dogs were assigned to 3 comparable groups on the basis of prostatic volume per kg of body weight and degree of prostatic hyperplasia determined histologically. Dogs in 2 groups were treated for 91 days (8 received 500 mg, PO, q 8 h [1,500 mg/d], and 6 received 100 mg, PO, q 8 h [300 mg/d]). The control group of 6 dogs did not receive medication. Effects of treatment on prostatic volume, prostatic weight, prostatic histologic characteristics, radiographic and ultrasonographic assessment of prostatic size, results of CBC, serum biochemical analyses, and urinalysis, serum testosterone concentration, and semen characteristics were determined. At the termination of the study, all dogs were euthanatized, and necropsies were performed. Investigators conducting tests and interpreting results were not aware of treatment group of each dog.

Results—Treatment did not affect prostatic weight, prostatic volume, or prostatic histologic scores, libido, semen characteristics, radiographs of the caudal portion of the abdomen, prostatic ultrasonographs, or serum testosterone concentrations. Results of CBC, serum biochemical analyses or urinalysis, and body weights did not change during treatment.

Conclusions and Clinical Relevance—Treatment with an extract of *S repens* for 91 days did not significantly affect the prostate gland of dogs. Adverse effects were not evident. Although products containing extracts of *S repens* are widely advertised for men with prostatic hyperplasia, beneficial or harmful effects of this plant extract were not found in dogs with prostatic hyperplasia. (*Am J Vet Res* 2000;61:880–885)

Prostatic hyperplasia is a common problem associated with aging in humans and dogs.[1-7] In men in the United States, current standard treatment for prostatic hyperplasia involves surgical (various types of transurethral prostatic ablation) or medical (use of 5-α-reductase inhibitor, an α-adrenergic antagonist, or both) intervention, depending on severity of clinical signs.[8-11] Because these treatments carry some risk of adverse effects and require oversight by a physician, a market exists for over-the-counter products.[12] In Europe, one of the most commonly used natural compounds in the treatment of men with voiding symptoms secondary to prostatic hyperplasia is a liposterolic extract of the berry of the saw palmetto plant (*Serenoa repens*).[12-14] Studies of efficacy in men suggest improvement in the condition, as determined on the basis of symptoms[12,15]; some studies also have documented improvement in objective measures such as urine flow rate and postmicturition residual volume.[15] Because benign prostatic hyperplasia also is common in dogs, and because owners and veterinarians can use over-the-counter products labeled for use in humans on their pets, we designed the study reported here to assess the efficacy of *S repens* in dogs with prostatic hyperplasia. We also attempted to determine whether the product had adverse effects in dogs at the doses used in the study.

Materials and Methods

Dogs—Twenty-five sexually intact adult male dogs were obtained from a commercial supplier.[a] They were primarily hound-type dogs and were estimated to be > 4 years old on the basis of tooth wear. Throughout the study, dogs were housed in runs (1 or 2 dogs/run).

Dogs had complete physical examinations, including per rectal palpation of the prostate gland. The estimated size, location, consistency, and symmetry of the gland were recorded. After withholding of food, a blood sample was obtained for a CBC and examination for microfilariae. Plasma concentrations of total protein, albumin, glucose, chloride, total carbon dioxide, sodium, potassium, calcium, and urea nitrogen and activity of alkaline phosphatase and alanine transaminase were determined. A urine sample for urinalysis and quantitative bacterial culture was obtained by cystocentesis or by transurethral catheterization, using aseptic technique. Dogs with anemia, thrombocytopenia, leukocytosis, hypoalbuminemia, hypoglycemia, hyperglycemia, moderate to severe electrolyte abnormalities, hypocalcemia, hypercalcemia, azotemia, macroscopic hematuria, pyuria, or urinary tract infection were excluded from the study. Criteria for urinary tract infection were > 100 bacteria/ml of urine collected by cystocentesis or > 1,000 bacteria/ml of urine collected via a urinary catheter. Of 25 dogs, 23 were acceptable for further evaluation.

Initial evaluation—Dogs were sedated with acepromazine maleate (0.1 mg/kg of body weight [maximum dose, 3 mg], SC) for radiography. The ratio between the width of

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the prostate gland and width of the pelvic canal measured at its widest point was calculated from ventrodorsal radiographic views of the caudal part of the abdomen. On the lateral view, ratio between the depth of the prostate gland and distance between the pubis and sacrum was calculated. Prostatic volume was estimated, using ultrasonography, and the pattern of prostatic echogenicity was recorded.

Anesthesia was induced by IV injection of thiamylal sodium and maintained with halothane administered via an endotracheal tube. Using aseptic technique, the prostate was exposed via a ventral midline incision that extended cranially from the pelvic symphysis. The prostate gland was measured independently by 2 investigators, using calipers to determine all 3 dimensions, and 2 needle biopsy[b] specimens were obtained, 1 from the right lobe and 1 from the left lobe. The abdomen was closed, and the dog was allowed to recover from anesthesia. Prostatic volume and prostatic volume per kg of body weight were calculated for each dog.

Biopsy specimens were fixed in neutral-buffered 10% formalin solution, embedded in paraffin, sectioned at a thickness of 5 nm, and stained with H&E. Microscopic examination of tissue was conducted to establish the degree of prostatic hyperplasia. Degree of hyperplasia was scored as follows: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe.

Of the 23 dogs from which a biopsy specimen was obtained, 20 with the most severe hyperplasia and the largest prostatic volume per kg of body weight were selected. All dogs had histologic evidence of prostatic hyperplasia except for 1, and that dog ranked ninth in prostatic volume per kg of body weight. The following additional tests were performed on these 20 dogs: radiography of the caudal portion of the abdomen, ultrasonography of the prostate gland, semen evaluation, and measurement of serum testosterone concentration.

Libido was assessed on the basis of ease of semen collection. Semen evaluation consisted of measurement of volume of the spermatozoa-rich component of the ejaculate, assessment of spermatozoa motility (scale of 0 to 20), quantitation of number of spermatozoa, evaluation of spermatozoa morphology (percentage of morphologically normal spermatozoa, percentage of spermatozoa with major abnormalities, percentage of spermatozoa with minor abnormalities), and quantitative bacterial culture of prostatic fluid. Prostatic fluid was considered infected when bacterial numbers exceeded 1,000 organisms/ml.

To assess serum testosterone concentration, 5 blood samples were collected from each dog at 30-minute intervals on the first morning of the study. Mean of the serum testosterone concentration, determined by use of radioimmunoassay, for these 5 samples was calculated for each dog.

Treatment—The 20 dogs were assigned to 3 comparable groups on the basis of prostatic volume per kg of body weight and histologic score for prostatic hyperplasia. Prior to treatment, groups did not differ significantly with regard to prostatic volume, prostatic volume per kg of body weight, or prostatic histologic scores. Dogs were treated orally 3 times daily at approximately 8 AM, 4 PM, and 7 PM for 91 days; first day of treatment was day 0. Treatments were assigned as follows: group A, 8 dogs that received *S repens* extract at a daily dose of 1,500 mg (five 100-mg capsules per treatment); group B, 6 dogs that received 300 mg of *S repens*/d (one 100-mg capsule per treatment); and group C, 6 dogs that did not receive medication. Capsules were provided to dogs in meatballs made of canned food; dogs of group C received meatballs 3 times daily that were made of canned food but did not contain capsules of medication.

Evaluation of treatment—Dogs were observed at least 3 times daily for evidence of abnormal clinical signs. During the midpoint (days 37 to 51) and again near the end (days 77 to 91) of the treatment period, the following evaluations were performed in the same manner as before treatment: complete physical examination, CBC, serum biochemical analyses, urinalysis, bacterial culture of a urine sample, radiography of the caudal portion of the abdomen, ultrasonography of the prostate gland, semen evaluation, bacterial culture of a semen sample, and determination of serum testosterone concentrations. Each type of evaluation was performed on all dogs on the same day (eg, all blood samples for serum testosterone concentrations were collected on the same day, and all ultrasonographic examinations were performed on the same day, but those days may not have coincided).

On day 92 or 93, dogs were weighed and then euthanatized, using a barbiturate overdose. Necropsy was performed on each dog. In dogs that had positive results for bacterial culture of urine or semen samples during the study, the abdomen was clipped and aseptically cleansed. Sterile instruments were used to incise the abdominal cavity. Urine then was collected by means of cystocentesis, and prostatic tissue was collected by use of a needle biopsy; those samples were submitted for bacterial culture. In dogs without evidence of infection in urine or semen, samples were not collected during necropsy for bacterial culture.

During necropsy, size of the prostate gland of all dogs was measured in situ independently by 2 investigators (JAB, DRF), using the same technique as before treatment. The prostate gland of each dog was removed and weighed. A biopsy specimen of prostatic tissue was collected, using the same technique that was used during the initial surgery. Biopsy specimens and the remainder of each prostate gland were fixed in neutral-buffered 10% formalin and processed for histologic examination. Testicular and epididymal tissues also were weighed and processed for histologic study. Any other organs in which abnormalities were suspected on the basis of results of analyses of blood or urine samples or that were considered abnormal during necropsy were processed for histologic evaluation.

Statistical analysis—For all tests, a value of $P < 0.05$ was considered significant. The product of the 3 dimensions of prostatic size was used to estimate prostatic volume. Pre- and posttreatment values for each group were compared, using a 1-way ANOVA and paired *t*-test. Weight of prostate gland per kg of body weight and per unit of body surface area were tabulated, and values from the 3 groups also were compared, using an ANOVA.

Histologic effects of treatment were evaluated by a pathologist (WAC) who was not aware of the group of origin of tissues. On completion of histologic evaluation, needle-biopsy specimens from the same dog were compared by the pathologist, again without knowledge of group of origin of the tissues. Data from histologic studies were evaluated by use of a 1-way ANOVA.

Results of other tests (CBC, serum biochemical analyses, urinalysis, serum testosterone concentration, semen evaluation, bacterial culture of urine and semen samples, radiography, and ultrasonography) also were assessed, such that those conducting the tests and evaluating the results were not aware of the treatment group for each dog. Only the investigators performing the physical examinations and observing the dogs daily were aware of the treatment group for each dog.

Results

Dogs—Two dogs of group A intermittently refused to voluntarily consume the medicated meatball, which required that they manually be given the

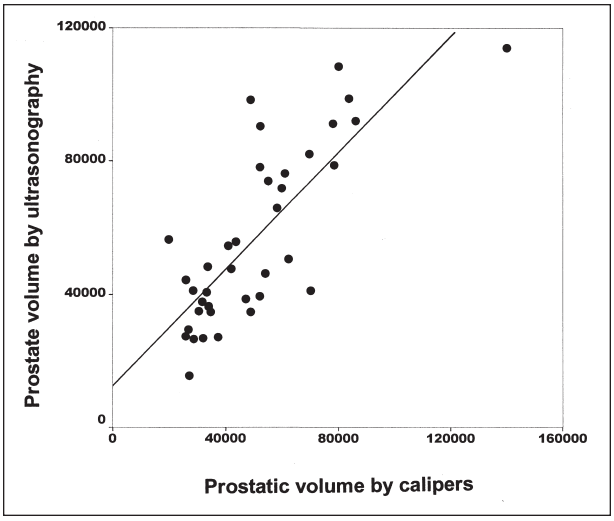

Figure 1—Comparison of prostatic volume and prostatic weight in a group of dogs with prostatic hyperplasia. Volume was measured in situ by use of calipers.

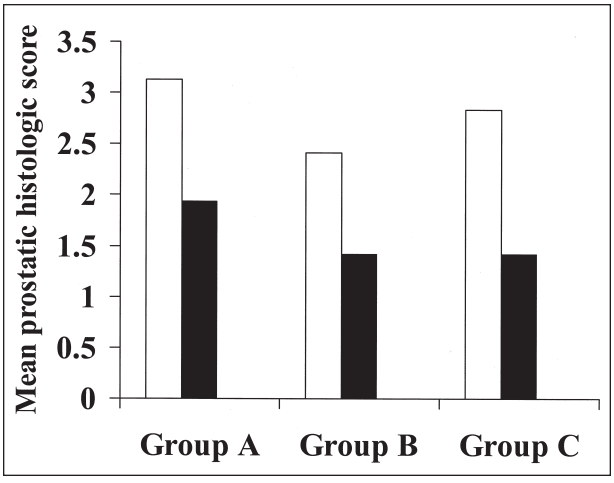

Figure 2—Effect of administration of *Serenoa repens* on histologic score of dogs with prostatic hyperplasia. Values were determined by histologic scoring of needle-biopsy specimens obtained before (□) and after (■) a 90-day treatment period. Group A = 1,500 mg/d. Group B = 300 mg/d. Group C = Untreated dogs.

capsules. Only 3 episodes of vomiting were recorded during the study; 1 dog in group A vomited once after treatment, and 1 dog in group C vomited twice after treatments. Other abnormal clinical signs were not detected. Prostatic size and consistency, as determined by palpation per rectum, did not change.

Body weight of dogs did not change significantly throughout the course of the study, regardless of treatment group. However, dogs of group C were significantly heavier (mean, 32.3 kg) than dogs of group A (mean, 26.5 kg) or B (mean, 27.9 kg) throughout the study.

Three dogs incurred traumatic injuries during the study. One dog was bitten by its penmate 4 days after initiation of treatment. That injury required general anesthesia of the dog to enable the wound to be cleaned, debrided, and sutured (with drains). Chloramphenicol was administered orally for 10 days. Five days after discontinuing chloramphenicol treatment, the dog had red urine. A urinary tract infection was confirmed by bacterial culture of a urine sample. The infection resolved after the dog was treated with orally administered trimethoprim-sulfamethoxazole for 10 days. A second dog developed a draining, swollen area on the left side of its face in the area located above the hemimandible on the 64th day of treatment. The area was cleaned, and the swelling resolved after the dog was given chloramphenicol orally for 14 days. The third dog was bitten by its penmate on the 76th day of treatment. The hair around the wounds was clipped and the wounds were cleaned, and they resolved after the dog was given trimethoprim-sulfamethoxazole orally for 14 days. That same dog lacerated the pad on one of its feet on the fence of the run on day 78, requiring the wound to be cleaned, sutured, and protected by a bandage.

Prostatic volume and weight—Treatment did not significantly affect prostatic volume ($P = 0.98$), prostatic volume per kg of body weight ($P = 0.76$), or prostatic weight ($P = 0.92$; **Table 1**). Prostatic volume, as determined by measurement of all 3 dimensions at the termination of the study, correlated well with prostatic weight ($r^2 = 0.88$; **Fig 1**), similar to results of a previous report.[16]

Histologic scores—At the end of treatment, histologic scores of prostatic tissue did not differ significantly among groups for biopsy specimens ($P = 0.77$) or for the entire gland ($P = 0.63$; **Fig 2**).

Seminal variables—Significant differences were not detected among treatment groups for any portion of the semen evaluation, including libido, seminal volume, spermatozoa motility, spermatozoa morphology, or spermatozoa concentration. Four dogs had positive results for bacterial culture of prostatic fluid prior to the treatment period. In 2 of these dogs, bacterial culture yielded negative results during the treatment period, despite lack of specific treatment. Two dogs continued to have positive results for bacterial culture of semen samples throughout the treatment period. One of these dogs developed a urinary tract infection with the same organism (*Escherichia coli*) sometime between day 45 and 90. Because the dog did not have clinical signs of infection, antimicrobial treatment was not instituted.

Serum testosterone concentration—Serum testosterone concentrations did not differ significantly among treatment groups at any time during the study (days 0, 45, or 90).

Radiography and ultrasonography—We did not detect a change in prostatic size or position of the gland during radiography of the caudal portion of the abdomen. Similarly, we did not detect changes in prostatic size or character by use of ultrasonography. Seven dogs had uniform echogenic patterns of the prostate gland, whereas 13 had intraprostatic cysts of variable size and number. Estimate of prostatic volume on the basis of ultrasonographic images cor-

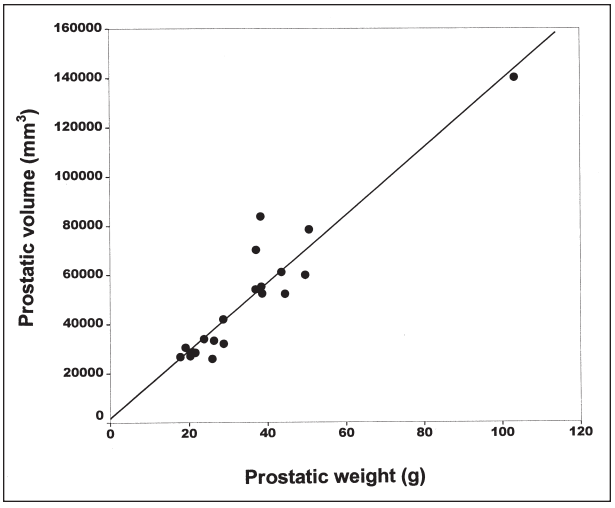

Figure 3—Comparison of prostatic volume (mm^3) measured in situ by use of calipers, compared with prostatic volume determined by use of ultrasonography.

related with actual measurement of prostatic volume by calipers ($r^2 = 0.62$; **Fig 3**).

Clinicopathologic evaluations—Abnormalities were not detected in association with treatment with *S repens*. Major abnormalities detected during CBC, serum biochemical analyses, and urinalysis were associated with dirofilariosis and consisted of eosinophilia, hyperglobulinemia, and mild proteinuria. Two dogs (1 each in groups A and B) developed moderate thrombocytopenia (50,000 to 100,000 cells/µl) during the treatment period. In 1 of those dogs, thrombocytopenia was associated with development of antibodies against the organism that causes Rocky Mountain Spotted Fever, whereas in the other dog, the change was associated with a urinary tract infection. In both dogs, platelet counts returned to within the reference range. Another dog developed a urinary tract infection without clinical signs during the treatment period. In that dog, $> 10^5$ streptococci/ml were cultured from a urine sample obtained via a urinary catheter on day 45, and $> 10^5$ staphylococci/ml were cultured from a urine sample obtained by cystocentesis on day 90. Antibiotics were not given to that dog at any time during the study.

Discussion

An extract of the berry of the saw palmetto or American dwarf palm tree (*S repens*, also known as *Sabal serrulata* or *Sabalis serrulatae*) is the most commonly used natural compound in the treatment of humans with abnormalities of urination secondary to benign prostatic hyperplasia.[12] This plant is native to the West Indies and the southeastern United States, growing in pine woods and sandy dunes along the coast of South Carolina, Louisiana, Georgia, and Florida.[17] The lipid extract of the dried fruit is used medicinally, as practiced historically by Native Americans, as a nutritional tonic and as medicine for genitourinary problems.[12] The extract is predominantly fatty acids and sterols. Active constituents are believed to be steroids chemically related to cholesterol, with the sitosterols believed to be most important.[12,18] The potential mechanism of action of this extract in prostatic hyperplasia is poorly understood.[12] Investigators have reported anti-androgenic properties at the level of prostatic cytosolic androgen receptors,[c,19] inhibition of 5-α-reductase,[d,20,21] or an estrogenic effect,[22,23] whereas other investigators have not confirmed these effects.[24-26] Some of the differences in those results may be attributed to the doses used.[12] Lack of consistency among those studies leaves potential mechanisms of action unclear.

Many studies have been conducted on the effectiveness of *S repens* in prostatic hyperplasia in humans; however, many have been uncontrolled studies.[12,15] Recent reviews of all controlled studies concluded that treatment with *S repens* improved urologic symptoms and urine flow measures, as compared with placebo treatment.[12,15] In 1 study that involved > 1,000 men,[27] *S repens* was compared with finasteride, but there were not any significant differences in subjective or objective measures of symptom scores between the groups treated with either of the products. Unfortunately, a control group was not included in that study. Because it was indicated in another recent study that finasteride was not better than use of a placebo,[9] comparing *S repens* to finasteride might only reveal equivalence to a placebo.[12] *Serenoa repens* has the same or fewer adverse effects, compared with that of other treatments.[12,15,17] Treatment with *S repens* does not decrease prostatic volume, concentration of prostatic-specific antigen, or serum concentrations of dihydrotestos-

Table 1—Mean (range) prostatic volume at the beginning and end of a 90-day treatment period and prostatic and testicular weights at the end of the treatment period in dogs receiving 1,500 mg/d (group A) or 300 mg/d (group B) of an extract of *Serenoa repens*, compared with values for untreated dogs (group C)

	Mean prostatic volume			
Treatment group	Before treatment (mm^3)	After treatment (mm^3)	Mean prostatic weight (g)	Mean testicular weight (g)
A	45,033 (19,766–77,971)	55,250 (27,074–83,700)	33.6 (19.1–50.6)	38.6 (24.0–59.2)
B	45,957 (28,131–86,084)	50,434 (26,752–140,081)	37.6 (17.8–103.3)	46.9 (37.6–58.1)
C	53,976 (33,626–80,013)	49,015 (25,870–70,139)	36.6 (23.8–49.6)	47.4 (44.8–58.4)

Values did not differ significantly ($P < 0.05$) in association with treatment.

terone.[12,24-26,27] A major problem with *S repens* treatment is that the products are sold as dietary supplements and are not monitored by an independent agency for safety, efficacy, or standardization within or between manufacturers.[8,12,15,17]

Dogs are the only other domestic animals that commonly develop prostatic hyperplasia as they grow older; the most effective treatment currently used is surgery (ie, castration). Furthermore, there has been an increased interest in the use of natural products in the treatment of diseases in veterinary medicine; thus, we studied whether this potentially safe, over-the-counter product would be efficacious in dogs. Unfortunately, at the doses and duration of administration used in the study reported here, it was not, although sample size was small. We did not detect any harmful effects. In pondering the reason that effects were not evident, we considered dose and duration of treatment. The dose used for studies in humans has been 320 mg/d (160 mg, PO, q 12 h).[12,15,27] Assuming the men weighed approximately 80 kg, the dosage used was 4 mg/kg/d. Our dogs ranged from 25 to 30 kg and received 300 mg (10 mg/kg/d) or 1,500 mg (50 mg/kg/d). Thus, assuming similar intestinal absorption and pharmacokinetics, the lack of effect does not appear to be associated with an insufficient dose. Most clinical trials in humans have lasted 1 to 3 months.[12,15] A significant improvement in symptoms in men has been detected as early as 2 weeks after initiation of treatment and was consistently evident by 6 to 8 weeks after treatment was begun, with a number of men reporting improvement in symptom scores increasing throughout longer study periods.[15,27] In 1 study in humans in which researchers found a decrease in prostatic size,[27] the maximum decrease was evident 13 weeks after initiation of treatment, whereas in another study,[28] increased urine flow rate was evident 60 days after initiation of treatment. Because the positive findings in those studies are within the same time frame as was used in our study, insufficient duration of administration seems an unlikely explanation for lack of efficacy.

Several explanations remain for lack of efficacy in the dogs of our study, compared with efficacy in humans. The response in humans could be a placebo effect that we could not document in our dogs, which did not have clinical signs of prostatic hyperplasia. In that case, it would appear that the disease must be sufficiently advanced to the point that it causes clinical signs at the time of treatment and any subsequent beneficial response. Conversely, the difference may be attributable to differences in the pathophysiologic mechanisms for the clinical signs produced by prostatic hyperplasia in the 2 species. It should be mentioned that our dogs, although they did not have clinical signs, did have moderate to severe prostatic enlargement, compared with that of mature male dogs in other studies (8,000 to 26,000 mm^3).[29,30] It is recognized that the main clinical signs in humans (ie, decreased peak and mean urine flow rate with increased residual urine volume) are not commonly evident in dogs. Those clinical signs may be attributable, at least in part, to adrenergic effects on surrounding smooth muscle, because men with those clinical signs also respond to anti-adrenergic treatment.[9] In a small study (63 patients),[31] investigators found that α-adrenergic antagonists were significantly more efficacious than *S repens*. The condition in humans also seems to be primarily stromal, whereas the condition in dogs seems to be primarily epithelial.[2,32]

The lack of efficacy of the extract of *S repens* in dogs is in contrast to efficacy for other drugs in dogs. The anti-androgenic drugs flutamide and hydroxyflutamide elicited a dose-dependent (2.5 or 5 mg/kg/d) decrease in prostatic size in mature male dogs that was evident ultrasonically as early as day 14 after initiation of treatment.[33] Finasteride, a 5-α-reductase inhibitor, at a dosage of 1 to 5 mg/kg/d, resulted in decreased prostatic size in dogs within 3 weeks[29,30,34]; the decrease in size was more pronounced by 15 to 16 weeks.[30,34,35] Higher dosages resulted in more pronounced decreases in size.[36] The doses of finasteride used in those studies were much higher than the dose used in humans (5 mg/d). The lowest dose that will reduce prostatic size in dogs with hyperplasia is unknown, but doses administered at the rate of 0.1 to 0.5 mg/kg/d did decrease serum dihydrotestosterone concentrations to a degree similar to that for 1 mg/kg/d.[37] It should be mentioned that finasteride is potentially teratogenic to male fetuses when pregnant women are exposed to the drug during the third month of gestation.[38] Several progesterone-type drugs also are efficacious in reducing prostatic size, although some also adversely affect gonadal function, depending on dose and duration of treatment.[39-43] Although such medical treatments are not as effective as castration in reducing prostatic size in dogs,[34,42] they do offer a medical alternative, albeit 1 that is not approved for this purpose, for owners who refuse surgery.

[a]Antech Inc, Barnhart, Mo.

[b]Tru-Cut Needle, Travenol Laboratories, Deerfield, Ill.

[c]Briley M, Carilla E, Fauran F. Permixon, a new treatment for benign prostatic hyperplasia, acts directly at the cytosolic androgen receptor in rat prostate (abstr). *Br J Pharmacol* 1983;79:327P.

[d]Bayne CW, Grant ES, Chapman K, et al. Characterisation of a new co-culture model for BPH which expresses 5 alpha-reductase types I and II: the effects of Permixon on DHT formation (abstr). *J Urol* 1997;157(suppl 4):194.

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