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Treatment of hypersexuality and benign prostatic hypertrophy with delmadinone acetate in intact male dogs

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Abstract: The aim of the present study was to evaluate the effectiveness of delmadinone acetate (DMA) for the treatment of hypersexuality (HS) and benign prostatic hypertrophy (BPH), which are frequently observed in male dogs, for which no surgical treatment has been indicated. The study was performed with 21 intact male dogs that had HS (n = 12) and signs of BPH (n = 9). DMA (Tardak® or Tardastrex®) was administered subcutaneously to each dog at a dose of 3-5 mg/kg and was repeated 15 days later as a second treatment. DMA administration was repeated in some cases until the clinical signs disappeared. The successful recovery rate of HS cases was found to be 50% after a single application and 25% by the second and third applications. The mean "recovery periods" and mean "stable periods" of these 3 consecutive applications were found to be 5.83, 7.66, and 6.00 days, and 16.7, 18.7, and 20.0 months, respectively. With regard to BPH after consecutive applications, treatment success rates, mean recovery periods, and mean stable periods were 33.3%, 22.2%, 44.4%, 12.0, 11.0, 9.5 days, and >30, 12, and 13.5 months, respectively. DMA is clinically applicable as a therapeutic agent for HS and BPH cases; however, repeated applications were required due to temporary recoveries.

Key words: Clinical application, prostate, repeated doses, therapeutic agent

Erkek köpeklerde hiperseksüalite ve benign prostat hipertrofisi'nin delmadinon asetat ile tedavisi

Özet: Erkek köpeklerde sıklıkla görülen ve cerrahi yaklaşımın endike olmadığı durumlarda, hiperseksüalite (HS) ve benign prostat hipertrofisi (BPH) olgularının tedavisinde delmadinon asetat'ın (DMA) etkinliği araştırıldı. Çalışma kısırlaştırılmamış 21 erkek köpekte yapıldı, bunların 12 tanesinde HS, 9 tanesinde de BPH semptomları gözlemlendi. DMA (Tardak® veya Tardastrex®) 3-5 mg/kg dozunda derialtı enjekte edildi ve 15 gün sonra ikinci tedavi aynı dozda yinelenildi. Gereken olgularda semptomlar ortadan kalkana kadar uygulamalar tekrar edildi. HS vakalarında iyileşme oranı tek enjeksiyondan sonra % 50, ikinci ve üçüncü enjeksiyondan sonra ise % 25 oranında bulundu. Sırasıyla bu semptomların

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ortadan kalkma süreleri 5,83, 7,66 ve 6,00 gün sürerken, semptomların yeniden ortaya çıkmadığı stabil kalma süresi, 16,7, 18,7 ve 20,0 ay olarak bulundu. BPH vakalarında iyileşme oranı sırasıyla: % 33,3; % 22,2; ve % 44,4; iyileşme süresi: 12,0; 11,0; ve 9,5 gün; ve iyileşmenin stabil kaldığı süreler: >30; 12 ve 13,5 ay olarak bulundu. DMA'nın HS ve BPH vakalarında klinik olgularda sağaltım amacı için uygun terapötik ajan olduğu fakat geçici süreyle sağladığı iyileşmeden dolayı tekrarlayan dozlarının uygulanmasının gerektiği kanısına varılmıştır.

Anahtar sözcükler: Klinik uygulama, prostat, tekrarlayan doz, terapötik ajan

Introduction

Hypersexuality (HS) is a condition that occurs in male dogs. Its clinical signs include mounting other objects and penile erection. Ejaculation, licking, and biting the penis and aggressive behavior may also be seen (1). In addition, thickening, inflammation, dermatitis, and wounds around the preputium may be observed in some cases (2).

The diagnosis of prostatic disorders is based on history, rectal or transabdominal palpation of the gland, the presence of urethral abnormalities, histological evaluation of biopsy material, and radiographic and ultrasonographic examination methods (3).

Examination of the prostate gland by caudo-abdominal palpation is more useful than digital rectal examination in canine species. A normal prostate gland has a symmetrical and smooth shape and is movable and painless (4,5).

For the evaluation of prostatic disorders, ultrasonography is a useful technique. As the prostate gland is not deeply positioned within the pelvic canal, it can be examined easily (3). Ultrasonographic examination can be performed by transabdominal, transrectal, perianal, or transurethral routes (6). The size, symmetry or asymmetry, and echogenic structure of the prostate gland may be evaluated together with the surrounding area and lymph nodes (5).

Benign prostatic hypertrophy (BPH) is a spontaneous and age-related condition in men, male dogs and apes (chimpanzee) (4,7). It was reported that canine prostate gland enlargement begins at 2.5 years of age (1). The prostate gland becomes enlarged in aging dogs and correlates with the size of the dog (6). Benign prostatic hypertrophy is observed in 95% of older dogs. In more than 80% of male dogs over 5

years of age with BPH, prostatic volume is 2 to 6.5 times greater than normal dogs (5).

In most cases of prostatic hypertrophy, clinical signs do not indicate abnormal or systemic problems. Hematological and urinary analyses may be in normal ranges (4,5). Clinical signs in affected dogs include serosanguineous prostatic fluid dripping from the tip of the penis, blood present in urine or semen, constipation, and dysuria (5).

Prostate hypertrophy is usually detected by ultrasonography as a uniformed enlarged mass. Echogenicity is observed in normal visual inspection. Small hyperechoic and anechoic areas may be identified (3,7). Prostatic parenchyma is observed as homogenous and increase in echogenicity (8,9).

Although castration is an effective treatment for BPH, medical treatment is still required for dogs that pose critical risks for surgery or that may subsequently be used for breeding (7,10,11).

Delmadinone acetate (DMA) is a progestin drug used for the treatment of prostatic hypertrophy, perianal tumors, and HS in male dogs as well as to prevent and suppress estrus in bitches (12). DMA is preferred mainly for both HS and BPH treatments because its anti-androgenic efficiency is higher than that of other progestogens (1,5,13).

The aim of the present study was to investigate the effectiveness of DMA on the treatment of HS and BPH cases by determining concurrent efficacy of its repeated doses on clinical signs.

Materials and methods

This study was performed with 21 intact male dogs of different breeds which had HS (n = 12; 2-11 years old) and BPH signs (n = 9; 8-13 years old), were referred to Clinic of Obstetrics and Gynecology,

Faculty of Veterinary Medicine, University of Ankara and therefore animals were grouped according to diagnosis.

Diagnosis of HS was based on history. Prostatic hypertrophies were diagnosed by history, digital rectal examination, cytology and ultrasound (linear probe, 6.0 MHz, Falco 100) applying the method described by Kamolpatana et al. (14). Echogenicity-homogeneity, symmetry, and the size of prostate were evaluated. BPH was diagnosed with ultrasonography, which displays smooth surface, homogeneity in parenchyma, and increased texture echogenicity.

Furthermore, fine-needle aspiration biopsy (FNAB) guided by transabdominal ultrasonography (15,16) was performed under sedation (0.3 mg/kg IV, Diazem[®]; Deva) and biopsy samples were stained with Papanicolaou's (17) staining technique. Thus, prostatic biopsy material was sampled solely from BPH cases.

DMA (Tardak[®] or Tardastrex[®]; Pfizer) was administered at a dose of 3-5 mg/kg subcutaneously and repeated after 15 days. In cases of neutrophil leukocyte infiltration in cytological samples, additional antibiotic tablets (enrofloxacin, 50 mg/3 kg BW, Baytril[®]; Bayer) were administered. DMA applications were repeated in some cases until the signs disappeared.

The time to disappearance of clinical signs in HS and BPH cases as well as regression of prostate size in BPH cases was defined as the "recovery period". Maintenance of sexual calmness was defined as the

"stable period". Even when the first treatment was sufficient, a second dose was administered 15 days later. The recovery period in HS cases was determined based on owner's observation, followed by an evaluation of patient's sexual behavior for 45 min at a minimum interval of 2-3 days in our clinic. Besides, the same intervals of evaluation to establish the "recovery period" in BPH cases and regression in prostate size were monitored using USG only in BPH cases not in HS cases. The stable period in all cases was determined according to history. Whenever animals exhibited the same signs, they were referred to the clinic again for re-evaluation.

Statistical analyses were performed using SPSS 14.0 with descriptive statistics and independent-sample t-test or paired-sample t-test methods.

Results

The results were evaluated separately for HS and BPH cases. Mounting the owner was described as the most frequent sign (91.7%) in HS cases. Penile erection was found at 66.7% of the time (Table 1). After the DMA treatment, 50% of the dogs were treated with the single dose and mean recovery time was 5.83 days. The success rates of the second and third treatments were both found to be 25% and mean recovery periods of these treatments were 7.66 and 6.00 days, respectively. The effectiveness of the first, second, and third DMA applications were found to be 16.7, 18.7, and 20.0 months, respectively (Table 2).

Table 1. Prevalence of clinical signs in HS and BPH cases.

Case	Clinical sign	x/n	Prevalence (%)
Hypersexuality	Mounting behavior	11/12	91.7
	Erection	8/12	66.7
	Odors	7/12	58.3
	Urine marking	3/12	25.0
	Epileptic forms	2/12	16.7
	Licking	1/12	8.3
BPH	Incontinentia urine	5/9	55
	Polyuria	5/9	55
	Hematuria	5/9	55
	Tenesmus	3/9	33
	Kyphosis	1/9	11
	Anorexia	1/9	11

Table 2. Prevalence of treated cases, mean recovery period, and stable period with respect to the number of applications in HS and BPH cases.

Case	Number of applications treated cases (%)	x/n period (day)	Prevalence of (Sx ± x)	Mean recovery period (month)	Mean stable period (Sx ± x)
BPH	1	3/9	33.33	12.0	> 30
	2	2/9	22.22	11.0 ± 1.4	12.0 ± 0.00 ^a
	3	4/9	44.44	9.5 ± 0.70	13.5 ± 4.44 ^a
HS	1	6/12	50	5.83 ± 1.72	16.7 ± 3.5
	2	3/12	25	7.66 ± 1.52	18.7 ± 4.9
	3	3/12	25	6.00 ± 1.00	20.0 ± 5.0

^aP > 0.05

The age distribution of dogs with HS symptoms was 2-5 years (n = 4) and 6-9 years (n = 8). Mean duration of clinical signs, mean stable period, and mean number of applications are summarized in Table 3. No significant difference was found between the stable periods of different age scales (P > 0.05).

In particular, clear ultrasonographic images were taken of the surface and edges of the prostate (Figure 1). No statistical differences were found between the data for prostatic size, and recovery and stable period in BPH cases as summarized in Table 4 (P > 0.05).

Histological examination of biopsy samples revealed different size of epithelial cells, erythrocytes, sparse neutrophil leukocytes, and no tumor-like cells (Figure 2).

The age of dogs with BPH ranged between 8 and 13 years. Incidence rates for different clinical symptoms in these cases were 55% for urinary incontinence, polyuria and hematuria, 33% for tenesmus, 11% for kyphosis, and 11% for anorexia (Table 1). For BPH, 33.3% (n = 3) of cases showed sexual calmness during clinical observation, but in

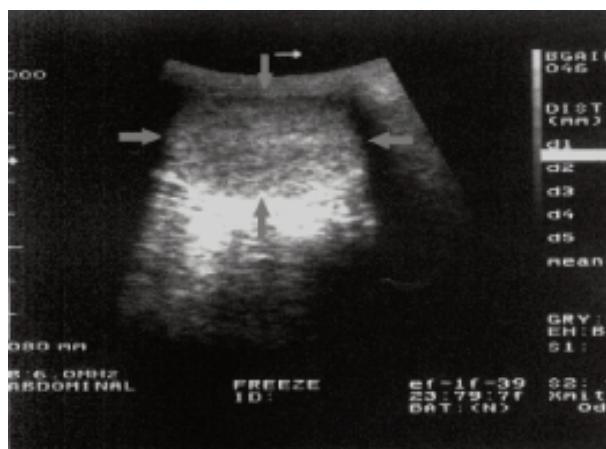


Figure 1. Ultrasonographic image of BPH shows a smooth surface, homogeneity in parenchyma, and increased texture echogenicity.

44.4% (n = 4) of the cases, clinical signs were observed 3 times during this period (Table 2).

In all BPH cases, the mean recovery period and mean stable period were found to be 9.2 days and 12.5 months, respectively. There were no significant differences between stable period and cases requiring 2 or 3 repetitions (P > 0.05).

Table 3. Distribution of HS cases with respect to age, mean stable period, and the number of applications.

Age (years)	n	Main duration of clinical signs (months) (Sx ± x)	Mean stable period (months) (Sx ± x)	Number of applications (Sx ± x)
2-5	4	4.0 ± 2.8	12.3 ± 6.7 ^a	1.5 ± 1.0
6-9	8	4.2 ± 1.3	9.3 ± 4.06 ^a	1.9 ± 0.8

^aP > 0.05

Table 4. Mean recovery period and stable period with respect to the size of prostate.

Size of prostate (cm)	n	Mean recovery period (days) (Sx ± x)	Mean stable period (months) (Sx ± x)
3.5 × 7.0 cm	6	8.5 ± 1.7 ^a	13.1 ± 2.2 ^b
> 3.5 × 7.0 cm	3	10.5 ± 2.1 ^a	14.5 ± 4.9 ^b

^aP > 0.05 ^bP > 0.05

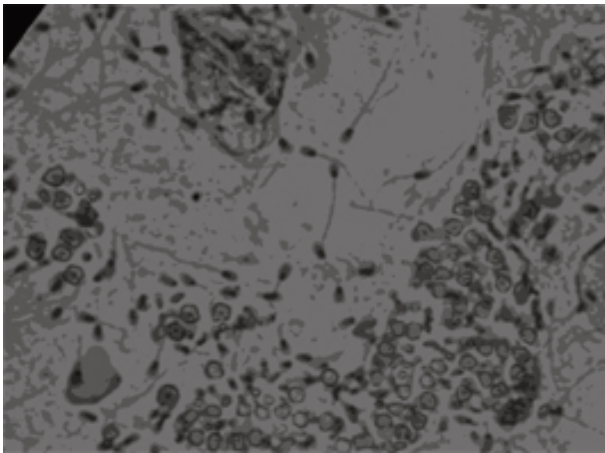


Figure 2. Cytological sample of a BPH case (different size epithelial cells, erythrocytes, and sparse neutrophil leukocytes).

Discussion

Signs of hypersexuality usually include excessive sexual activity, such as mounting of people or objects, erection, ejaculation, and sometimes epileptic behavioral changes (1,18). HS can be accompanied by aggressiveness, psychological restlessness, and epileptic seizures (19).

In this study, mounting the owner was the most common sign and its rate was as high as 91.7%. Erections were also found to occur at a rate of 66.7% and forms of epilepsy were found at a rate of 16.7%.

Synthetic progestins cause a decrease in prostate size in dogs with BPH by suppressing gonadotropin release and plasma T-concentration due to its negative feedback effect on the pituitary gland (20). Medical indications for progestin administration also include canine HS (13).

Successful recovery rate after the first treatment (average: 16.7 month) was found to be 50%. Other cases required second (25%) and third (25%)

treatments. This result shows that the effect of DMA is reversible in HS; therefore, application of DMA should be repeated. Arbeiter (1) reported that application of DMA should be repeated every 5 or 6 months. In this study, we waited for the recurrence of signs in order to avoid known side effects of frequent application of DMA. This study showed that waiting for recurrence after the first treatment could help to avoid drug side effects during the treatment period.

BPH, which is the enlargement of the prostate gland without inflammation, is related to age (21). Initially, dogs with BPH may not have any clinical signs. In this study, dogs with hematuria (55%) and tenesmus (33%) were observed to be more frequent.

Glandular hypertrophy can be seen in 2.5 year old dogs with BPH; prevalence increases at 4 years of age and the frequency of BPH reaches 80% by age 6 and 95% by age 9 (21). In this study, dogs that were brought to our clinic with signs of BPH were between 8-13 years old. These ages constitute the most critical period for BPH and also its signs can clearly be seen in this period, as reported by Berry et al. (21).

The normal size of the prostate is 1.7 cm × 2.5 cm in adult male dogs but it is variable considering to breed, age, and body weight (7,22). The lengths and widths of prostates in dogs studied by ultrasonographic measurement were found to be higher than 3.5 cm and 7.5 cm, respectively. Our findings showed that the recovery time and stable period were not related to prostatic size in BPH cases (P > 0.05). Some authors reported that clinical signs of recovery were detected between 7 to 10 days and also that the recovery period was not related to prostatic size (13,21). In this study, the mean time to disappearance of clinical signs was 9.2 days and no correlation was found between prostate sizes and recovery period.

In the present study, normal epithelial cells, erythrocytes and neutrophils were detected by means of FNB, which was applied for confirming the ultrasonographic findings in BPH cases. Anisocytosis, karyokinesis, presence of vacuoles, and no basophilic variation in cytoplasm have been used for differential diagnosis between BPH and prostate carcinoma with cytological analysis (16). These methods were not used in our study, because the present study was carried out on animals with only BPH.

All of the dogs in our study had owners who did not accept the castration operation because of its complications (senility-anesthesia, side effects, and postoperative aggressiveness). Hormonal treatment could be an alternative for BPH cases. The effectiveness of estrogen and progesterone treatment in prostate hypertrophy has been substantiated by some authors (23). It was reported that in BPH cases, even though administration of DMA (1-2 mg/kg) results in remission of clinical signs within 4 days, repetition of the dose is required a week later; which is effective for at least 3 months (24). In our study, disappearance of clinical signs occurred in HS cases in between 5.83 and 7.66 days and in BPH cases in between 9.5 and 12.0 days. Similarly, disappearance of HS signs in 2-5 days after DMA application and maintenance of sexual calmness for 3-5 months were reported (19).

Average values obtained in the present study indicate no recurrence of clinical signs for at least 4-5 months, which concurs with results reported by other authors (13).

In a previous study where medroxyprogesterone acetate and D-chlormadinone acetate were used for treating BPH cases as an alternative to castration, it was reported that in most of the dogs, clinical signs could recur 3 to 24 months after the initial treatment (11,13). In the present study, recurrence of clinical signs was not seen for 12.0-13.5 months and a continuation of prostatic regression was also observed. In HS cases, no clinical signs were observed for 16.7 to 20.0 months. No statistically significant difference was found between DMA administered 3 times at different interval durations ($P > 0.05$).

This treatment protocol is never as successful as castration and requires repeated injections (13). Repetition of signs following the administration of a single DMA injection after 30 months was found to be 33%, which is similar to findings of other authors. Secondary and tertiary repetitions were required for 22.22% and 33.33% of the remaining cases, respectively.

In conclusion, DMA is clinically applicable as a therapeutic agent for cases of HS and BPH when castration is not an option; however, repeated applications are required.

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