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Original article

The effects of osaterone acetate on clinical signs and prostate volume in dogs with benign prostatic hyperplasia

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Abstract

A clinical trial was performed to evaluate the therapeutic efficacy of osaterone acetate (OSA) in the treatment of benign prostatic hyperplasia (BPH) in dogs. Osaterone acetate (Ypozane, Virbac) was administered orally at a dose of 0.25 mg/kg body weight once a day for seven days to 23 dogs with BPH. During the 28-day trial, the dogs were monitored five times for their clinical signs and prostate volume. The OSA treatment promoted rapid reduction of clinical scores to 73.2% on day 7 and to 5.9% on day 28 ($p<0.05$). Osaterone acetate induced the complete clinical remission in approximately 83.0% of the dogs on day 28. The prostate volume regressed to 64.3% of the pretreatment volume after two weeks of the treatment ($p<0.05$) and to 54.7% at the end of the trial ($p<0.05$). In conclusion, OSA quickly reduced clinical signs and volume of the prostate glands in dogs with BPH.

Key words: dogs, benign prostatic hyperplasia, osaterone acetate, prostate volume

Introduction

Benign prostatic hyperplasia (BPH) is the most common disease of the prostate gland in dogs. More than 80% of intact male dogs older than 5 years exhibit BPH, and prostatic volume in affected dogs is 2 to 6.5 times greater than that in normal dogs of similar weight (Johnston et al. 2000, Parry 2007, Smith 2008). Medium- and large-sized breeds are prone to the development of BPH. This condition is associated with the proliferation (hyperplasia) and increased cell volume (hypertrophy) of the prostatic tissue.

Benign prostatic hyperplasia begins as glandular hyperplasia and subsequently transforms to cystic hyperplasia with the formation of multiple small cysts within the prostatic parenchyma. The etiology of BPH is not fully understood, but dihydrotestosterone (DHT) is known to play a key role in its pathogenesis. Testosterone is the major androgen secreted from the testes but DHT, formed from testosterone by the enzymatic action of 5-α-reductase in prostatic epithelial cells, is the main androgen that mediates the development and growth of the prostate. With age, the concentrations of DHT and its receptors increase in prostatic tissue (Johnston et al. 2000, Gobello and Corrado 2002, Andriole et al. 2004). Other androgenic and/or

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oestrogenic hormones and mitogenic growth factors may also be implicated in the pathogenesis and/or the progression of the disease.

Nearly all intact male dogs may develop BPH with age, but many patients do not exhibit clinical signs of the disease. When present, clinical signs of BPH include serosanguinous urethral discharge not associated with urination, flattened faeces, tenesmus, difficult urination, haemospermia and claudication of hind limbs (Johnston et al. 2000, Gobello and Corrado 2002, Smith, 2008).

Canine BPH can be treated by surgical or pharmacological methods. Surgical methods are used in non-breeding dogs. Pharmacological treatment is an alternative for breeding dogs and old animals with associated diseases. Drugs for BPH treatment include progestagens, oestrogens, antioestrogens and 5a-reductase inhibitors. The use of androgen receptor antagonists with osaterone acetate (OSA) for BPH treatment has been recently described in the literature (Niżanski et al. 2014).

Preclinical studies revealed that OSA is a promising treatment for BPH in dogs (Murakoshi et al. 1992, Tsutsui et al. 2000, Tstutsui et al. 2001). However, the effectiveness of OSA in the treatment of canine BPH has been confirmed by few clinical studies (Albouy et al. 2008, Błasiak et al. 2010). Thus, the aim of this clinical trial was to evaluate the effectiveness of OSA treatment in reducing clinical signs and prostate volume in dogs with BPH.

Materials and Methods

Animals

A total of 23 dogs aged 6 to 13 years were initially included in this study. The animals belonged to eight different breeds: Dachshund (4), German Shepherd (4), American Staffordshire Terrier (3), Bernese Mountain Dog (3), Yorkshire Terrier (3), West Highland White Terrier (3), Rottweiler (2) and Doberman (1). The dogs were qualified for the trial if they met the following two criteria:

The presence of at least one of four clinical signs:

1) urethral blood discharge without urination;
2) constipation or tenesmus;
3) urination related problems (difficult urination/ incontinence);
4) mobility difficulties;

The increase in prostate volume, as determined by transabdominal ultrasonography.

The dogs were patients of the Clinic of the Department of Animal Reproduction, Faculty of Veterinary Medicine, University of Warmia and Mazury in Olsztyn. Written consent from the owners was received for each animal. The animals were kept under normal housing conditions and were fed commercial diet. They were brought to the University Clinic to attend scheduled monitoring visits. The experiment was carried out according to Good Clinical Practice guidelines.

Drugs and treatment

Osaterone acetate (Ypozane; Virbac) tablets with four dosage units were used due to differences in the body weights of the examined dogs. The drug was administered orally by the owner at the target dose of 0.25 mg/kg body weight once a day, within half an hour after feeding, for seven days.

The dogs were not administered any other drugs that could affect the biosynthesis, action or metabolic pathway of androgenic hormones during the trial.

Monitoring

Five visits were scheduled during the 28-day trial: the first visit on day 0, the second visit on day 7 ± 2, the third visit on day 14 ± 2, the fourth visit on day 21 ± 2, and the fifth visit on day 28 ± 2. Day 0 was the first day of treatment with OSA. During each visit, clinical signs of BPH were monitored, and clinical scores were obtained by summing up the scores for the four clinical signs on a scale of 0 to 2 points, depending on its severity. Clinical recovery or complete remission was defined as a clinical score of 0 combined with reduction in the volume of the prostate gland.

Transabdominal examinations were performed on dogs positioned in dorsal recumbency, with an empty bladder and rectum. The entire prostate gland was examined with the MyLab Gold Vet scanner (Turin, Italy) with a microconvex probe using a frequency range of 5.0 – 6.6 – 7.5 MHz after the application of ultrasonography gel. The prostate was scanned during each visit, and the length (L), width (W) and dorsoventral diameter (H) of the prostate were measured.

Prostate volume (Vp) was estimated according to the formula of Kamolpatana et al. (2000): $Vp\ (cm3) = (L \times W \times H)/2.6 + 1.8$.

Statistical analyses

Patient data were compiled in an Excel spreadsheet file (Microsoft Corporation, Seattle, USA). Descriptive analyses were performed using the descriptive function in the R package (version 3.4.4, 2018). The degree of clinical recovery in each symptom group was compared between visits using Cochran's Q test and McNemar's test. The Friedman test with Bonferroni adjustment was used to determine differences in

Table 1. The effect of OSA treatment on clinical sores (n/%) in dogs with BPH.

Clinical sign	Score	n (%) Day 0	7	14	21	28
Urethral blood discharge without urination	0 Absent	12 (53.2)[a]	13 (56.5)[a]	18 (78.3)[b]	20 (87.0)[b]	23 (100)[b]
	1 Occasional	2 (8.7)	5 (21.7)	2 (8.7)	1 (4.3)	0 (0.0)
	2 Frequent	9 (39.1)	5 (21.7)	3 (13.0)	2 (8.7)	0 (0.0)
Constipation or tenesmus	0 Absent	7 (30.4)[a]	11 (47.8)[b]	15 (65.2)[b]	16 (69.6)[b]	19 (82.6)[b]
	1 Occasional	6 (26.1)	6 (26.1)	5 (21.7)	7 (30.4)	4 (17.4)
	2 Frequent	10 (43.5)	6 (26.1)	3 (13.0)	0 (0.0)	0 (0.0)
Urinary problems (difficult urination/incontinence)	0 Absent	11 (47.8)[a]	11 (47.8)[a]	21 (91.3)[b]	23 (100)[b]	23 (100)[b]
	1 Occasional	3 (13.0)	7 (30.4)	2 (8.7)	0 (0.0)	0 (0.0)
	2 Frequent	9 (39.1)	5 (21.7)	0 (0.0)	0 (0.0)	0 (0.0)
Movement problems	0 Absent	10 (43,5)[a]	14 (60.9)[b]	16 (69.6)[b]	19 (82.6)[b]	22 (95.7)[b]
	1 Occasional	7 (30.4)	5 (21.7)	4 (17.4)	2 (8.7)	1 (4.3)
	2 Frequent	6 (26.1)	4 (17.4)	3 (13.0)	2 (8.7)	0 (0.0)

a, b – values in the same row with different superscript letters differ significantly at $p<0.05$

prostate volume between follow-up visits. The statistical analysis was performed using IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY, USA: IBM Corp.)

Results

Clinical scores

Individual and total scores for the four evaluated clinical signs are shown in Table 1. Constipation and tenesmus were the most common signs of BPH, which were detected in 69.6% of the dogs. Other clinical signs were less frequently observed with mobility difficulties in 56.5%, urination related problems in 52.1 %, and urethral blood discharge without urination in 47.8% of the patients. On day 7, a statistically significant ($p<0.05$) decrease in the severity of constipation and mobility difficulties was observed relative to the first visit, and on day 14 – in the severity of urethral blood discharge and urination related problems.

Osaterone acetate treatment resulted in a rapid reduction of mean percentage scores to 73.2% on day 7 and to 5.9 % on day 28 ($p<0.05$; Fig. 1). By the end of the 28-day trial, OSA had induced complete clinical remission in approximately 82.6% of the dogs (Fig. 2).

Severe adverse effects were not observed in any of the patients subjected to OSA treatment. However, a transient increase in appetite (4/23 – 17%) and apathy (3/23 – 13%) were observed in several dogs during the first week of the treatment.

Prostate volume

The examined dogs differed considerably in the size of the prostate gland, and the percentage reduction in prostate volume induced by OSA was evaluated. Prostate volume decreased significantly ($p<0.05$) to 64.3% after two weeks of the treatment, and to 54.7 % on day 28 (Fig. 3).

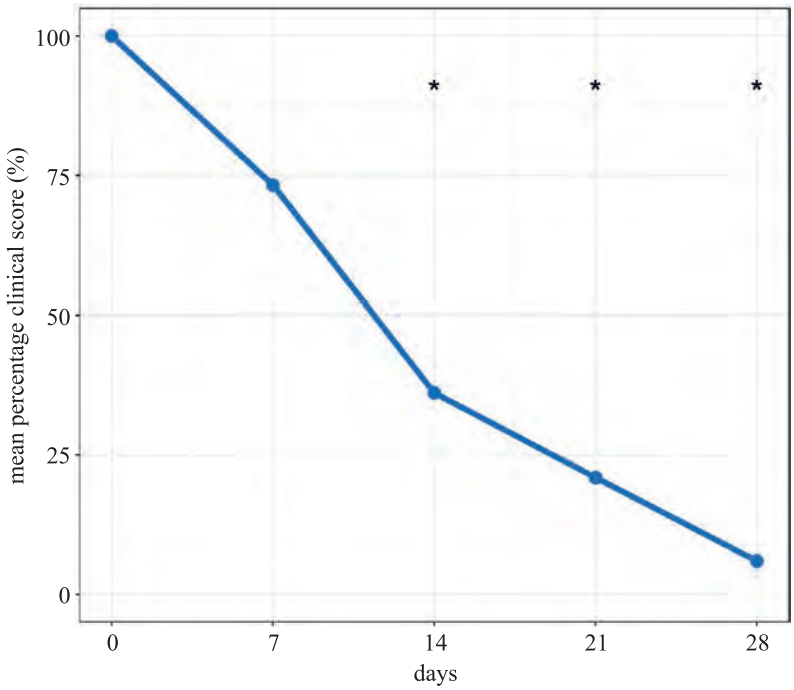

Fig. 1. Mean percentage clinical score in dogs with benign prostatic hyperplasia (BPH) (n = 23) treated with osaterone acetate (OSA). * values marked with asterisk differ significantly at $p<0.05$ relative to day 0

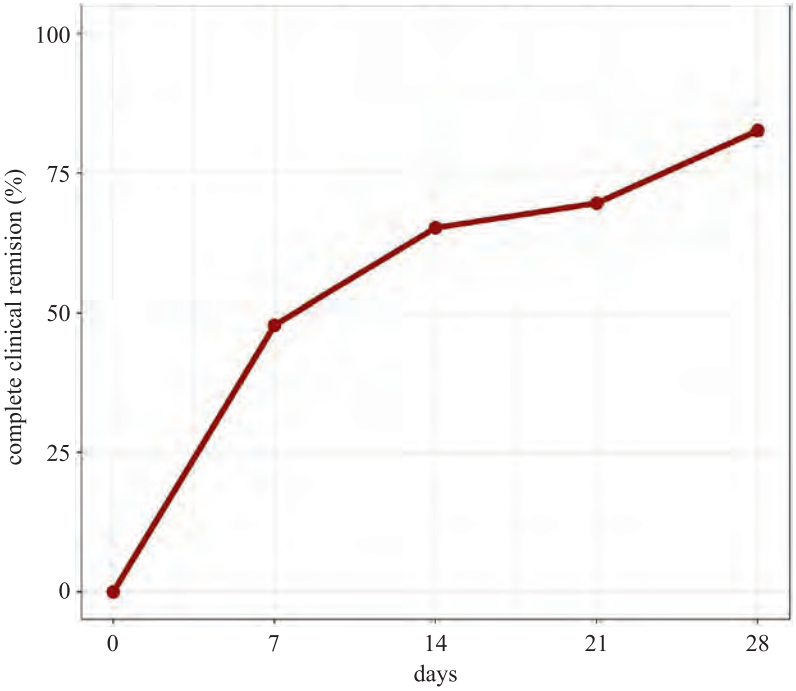

Fig. 2. Complete clinical remission (%) in dogs with benign prostatic hyperplasia (BPH) (n = 23) treated with osaterone acetate (OSA).

Discussion

In the present study, OSA treatment administered to dogs with BPH resulted in a rapid reduction of clinical signs. In a study by Albouy et al. (2008), OSA also rapidly decreased clinical scores to 73.2% on day 7 and to approximately 6.0% on day 28. Błasiak et al. (2010) reported that the clinical signs of BPH had disappeared after several days of the treatment in 39 out of 40 dogs.

Complete clinical remission was achieved in approximately 83.0% of the dogs. A similar remission rate was reported by Aublay et al. (2008) in patients administered OSA daily for 7 days.

The volume of the prostate gland and changes in

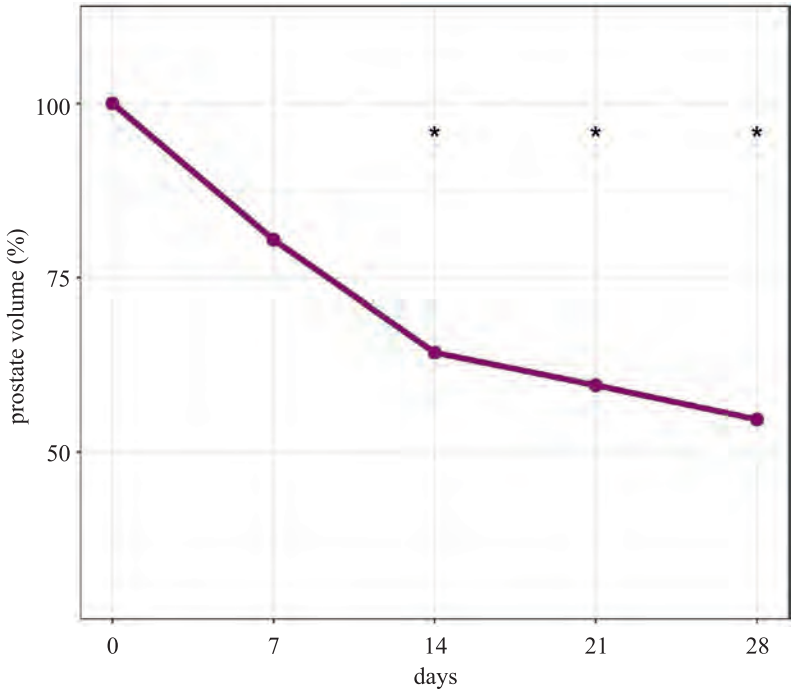

Fig. 3. Mean percentage reduction in prostate volume in dogs with BPH (n = 23) treated with osaterone acetate (OSA).
* values marked with asterisk differ significantly at $p<0.05$ relative to day 0

echogenicity provide a consistent and reliable indication of BPH. In the present study, prostate volume decreased significantly after 14 days of OSA treatment to approximately 64.3% of the pretreatment volume. Tsutsui et al. (2001) administered OSA at a dose of 0.2 and 0.5 mg to 5 dogs with BPH for one week. The average prostatic regression rate was 62.6% after two weeks of the treatment. In a study by Albouy et al. (2008), the percentage reduction in prostate volume was 38.0% on day 14. A rapid decrease in the size of the prostate gland was also reported by Tsutsui et al. (2000) and Błasiak et al. (2010).

The 28-day trial, during which dogs undergoing OSA treatment were monitored for clinical signs of BPH, provided valuable practical information. Rapid patient recovery and the elimination of symptoms are very important from the clinical point of view. Rapid remission of disease symptoms is also expected by animal owners. The present study has important implications for both veterinarians and dog owners.

Osaterone acetate has potent antiandrogenic activity. It impairs the uptake of DHT in the prostate gland and inhibits the action of 5a-reductase. Furthermore, OA directly decreases the concentrations of DHT and the androgen nuclear receptor in the prostate (Takezawa et al. 1992, Tsutsui et al. 2000, Tsutsui et al. 2001). The administration of OSA does not decrease the plasma levels of luteinising hormone (LH) (Tsutsui et al. 2000) and does not affect the testes or pituitary LH cells (Murakoshi et al. 1992). The drug's ability to rapidly reduce clinical signs and prostate volume can probably be attributed to its pharmacokinetic properties. In beagle dogs with OSA orally administered daily for one week, its peak serum concentration was reached on day 7 and returned to the basal level after 21 days (Allix et al. 2006). Osaterone acetate does not significantly impair spermatogenesis and the treated stud dogs remained fertile (Tsutsui et al. 2001, Błasiak et al. 2010).

In conclusion, our clinical study demonstrated that OSA rapidly reduced clinical signs and the volume of prostate glands in dogs with BPH.

References

Albouy M, Sanquer A, Maynard L Eun HM (**2008**) Efficacies of osaterone and delmadinone in the treatment of benign prostatic hyperplasia in dogs. Vet Rec 163: 179-183.

Allix V, Sillon M, Mezzasalma T, Maynard L (**2006**) Pharmacokinetics of osaterone acetate after repeated oral administration at 0.25 mg/kg/day for 7 days. Proceedings 31st World Small Animal Veterinary Congress. Prague, Czech Republic, October 11 to 14, p. 834.

Andriole G, Bruchovsky N, Chung LW, Matsumoto AM, Rittmaster R, Roehrborn C, Russell D, Tindall D (**2004**) Dihydrotestosterone and the prostate: the scientific rationale for 5alpha-reductase inhibitors in the treatment of benign prostatic hyperplasia. J Urol 172: 1399-1403.

Błasiak K, Antończyk A, Mikołajewska N, Ochota M, Stańczyk E, Niżański W (**2010**) The effectiveness

of osaterone acetate treatment on prostatic regression in dogs with benign prostatic hyperplasia (BPH). Reprod Domest Anim 45 (Suppl 3): 79.

Gobello C, Corrada Y (**2002**) Noninfectious prostatic diseases in dogs. Compend Contin Educ Vet 24: 99-107.

Johnston SD, Kamolpatana K, Root-Kustritz MV, Johnston GR (**2000**) Prostatic disorders in the dog. Anim Reprod Sci 60-61: 405-415.

Kamolpatana K, Johnston GR, Johnston SD (**2000**) Determination of canine prostatic volume using transabdominal ultrasonography. Vet Radiol Ultrasound 41: 73-77.

Murakoshi M, Inada R, Tagawa M, Makino M, Suzuki M, Mieda M, Honma S, Takezawa Y, Yamanaka H (**1992**) Inhibitory influence of a new steroidal anti-androgen, TZP-4238, on prostatic hyperplasia in the beagle dog. Acta Pathol Jpn 42: 151-157.

Niżański W, Levy X, Ochota M, Pasikowska J (**2014**) Pharmacological treatment for common prostatic conditions in dogs – benign prostatic hyperplasia and prostatitis: an update. Reprod Domest Anim 49 (Suppl 2): 8-15.

Parry NMA (**2007**) The canine prostate gland: part 1. Non-inflammatory diseases. UK Vet Companion Animal 12: 1-4.

Smith J (**2008**) Canine prostatic disease: a review of anatomy, pathology, diagnosis, and treatment. Theriogenology 70: 375-383.

Takezawa Y, Fukabori Y, Yamanaka H, Mieda M, Honma S, Kushitani M, Hamataki N (**1992**) Effects of a new steroidal antiandrogen TZP-4238 on hormone-induced canine prostatic hyperplasia. Prostate 21: 315-329.

Tsutsui T, Hori T, Shimizu M, Orima H, Kawakami E, Fukuda S (**2000**) Regression of prostatic hypertrophy by osaterone acetate in dogs. J Vet Med Sci 62: 1115-1119.

Tsutsui T, Hori T, Shimizu M, Tatsuzawa C, Kawakami E (**2001**) Effect of osaterone acetate administration on prostatic regression rate, peripheral blood hormone levels and semen quality in dogs with benign prostatic hypertrophy. J Vet Med Sci 63: 453-456.