Regression of Prostatic Hypertrophy by Osaterone Acetate in Dogs

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ABSTRACT. The prostatic regression effect of oral administration of a new steroidal anti-androgen, osaterone acetate, was investigated in dogs with prostatic hypertrophy. To dogs with prostatic hypertrophy, 0.1–1.0 mg/kg of osaterone acetate was orally administered for one week, and the regression rate was observed. It was shown that administration of osaterone acetate at 0.2 mg/kg or higher, sharply regressed prostatic hypertrophy during the early stage. Therefore, this agent may be clinically applicable as a therapeutic agent for benign prostatic hypertrophy.

KEY WORDS: benign prostatic hypertrophy, canine, osaterone acetate.

In dogs, the prostate hypertrophy was reported to develop by four years of age by Schloetter and Bollman [16], and by six years of age by Brendler et al. [3]. Berry et al. also reported that 95% of dogs at nine years of age or older showed benign prostatic hypertrophy (BPH) and they considered this to be a normal physiological change in intact male dogs [2].

As clinical symptoms of BPH in dogs, hematuria, dysuria, and dorsal curvature or claudication of hindlimbs due to pain are observed [4]. Krawiec and Hefflin reported that the incidence of prostatic diseases (most are BPH) in intact dogs accounted for 6.2% of all diseases in male dogs of four years of age or younger, 17.5% in those of 4–7 years of age, 32.8% in those of 7–10 years of age, and 43.5% in those of 10 years of age or older [11]. Therefore, BPH is the predominant geriatric disease in intact male dogs.

It is known that because the prostate is an androgen (A) -dependent organ, isolation of the testes which are a source of A secretion, causes prostatic atrophy. Therefore, castration is applied for treating BPH in dogs [16]. Other than castration, administration of estrogen [12], anti-A agents [1, 6, 14], and GnRH antagonists [21] are being investigated. We previously reported a method in which a combination of an oral anti-A agent, chlormadinone acetate (CMA), and an implant agent (GS implant®, Teikoku Hormone Mfg. Co., Ltd., Tokyo) is administered to improve clinical symptoms during the early stages of BPH, and to inhibit BPH for a prolonged period [8–10, 13, 17].

A recently developed new steroidal anti-A, 17 α-acetoxy-6-chloro-2-oxa-4,6-pregnadiene-3,20-dione (osaterone acetate) has been reported to show a five-fold stronger effect of regressing the prostate than CMA [18]. Tsumagari et al. used tablets of this agent (containing 5 mg of osaterone acetate with a diameter of 6.5 mm and 10 mg in weight) to treat dogs with BPH and showed that it reduced the clinical symptoms during the early stage and the effect persisted for a prolonged period [9]. However, in their study, the relationship between the dosage and the rate of change in prostatic volume was not clear because osaterone acetate was administered in a broad dosage [19]. Therefore, we designed this study to clarify the dosage for oral administration of osaterone acetate to regress the prostate during the early stage using dogs with BPH. Furthermore, time-course changes in the plasma osaterone acetate level after administration and the effects on peripheral blood sex hormone levels were also observed.

Animals: Eighteen intact male dogs used in the experiment were selected from 27 beagles of 9–14 years of age bred and maintained at our colony. The dogs were selected by clinical findings, rectal examination, and lateral radiography (X-ray) performed twice with a one-week interval. Dogs that were excluded from the experiment were six dogs (22.2%) in which the most part of the prostate was located in the pelvic cavity, one dog showing an unclear shadow of the prostate on X-ray examination (3.7%), and two dogs (7.4%) in which the prostatic hypertrophy was not clear.

The age and weight of the 18 dogs used in the experiment were 9–13 years (mean ± SE: 10.1 ± 0.3 years) and 9.1–16.6 kg (13.2 ± 0.5 kg), respectively. Of these dogs, BPH accompanied by hematuria was observed in six dogs, and the age and weight of these dogs were 9–13 years (10.0 ± 0.7 years) and 10.7–16.6 kg (13.4 ± 0.9 kg). These dogs were individually kept in cages in an animal room in which the temperature was maintained at 20 ± 2°C, and the dogs were fed commercial dog food. Their general condition was observed twice a day, in the morning and evening.

Administration of osaterone acetate: For the administration, 0.1, 0.2, 0.5, and 1.0 mg/kg of osaterone acetate were administered to 4, 4, 4, and 3 dogs, respectively. The control group consisted of three untreated dogs. To each group, 2, 2, 0, 1, and 1 dog with BPH were allocated. The duration of administration was seven days in all groups, and the drug was administered orally. To the control group, tablets containing the same base excluding osaterone acetate were adminis-
tered.

Measurement of the prostatic size: Regarding the size of the prostate, the length (L) and height (H) were measured by X-ray examination, and the oral areas were calculated from these values and compared. The prostate was observed prior to, and one week, two weeks, and one, two, three and four months after administration of osaterone acetate. In X-ray of dogs in which the prostate was partially located in the pelvic cavity, a glass tube was inserted into the rectum to press the prostate into the abdominal cavity.

Measurement of peripheral blood osaterone acetate, LH, and testosterone levels: Blood samples for measurements of the peripheral blood osaterone acetate, LH, and testosterone levels were collected on the same days as X-ray. Three milliliters of blood were collected three times a day (9:30, 13:30, 15:00) from the anterior brachiocephalic vein. The blood samples were immediately centrifuged at 600G for 20 min, and the plasma samples were stored at −30°C until measurement of hormones. The plasma osaterone acetate level was measured by GC-MS [7], and the LH and testosterone levels were measured by RIA [10]. For measurement of osaterone acetate, plasma samples collected at 9:30 were used. Because daily variations in LH and testosterone levels are large [10, 20], the values were obtained three times a day, and the mean value was regarded as the value for that day.

The rate of change in prostatic area (RCPA) after osaterone acetate administration: RCPA prior to and after administration of osaterone acetate at each dose is shown in Fig. 1, with the areas prior to administration regarded as 100%.

The mean prostatic areas prior to osaterone acetate administration were 14.8 ± 1.7 cm², 12.6 ± 1.3 cm², 14.8 ± 1.6 cm², 15.4 ± 2.1 cm², and 11.8 ± 1.6 cm² in the 0.1 mg/kg, 0.2 mg/kg, 0.5 mg/kg, 1.0 mg/kg, and control groups, respectively. The mean area of the prostate of six dogs with BPH was 14.3 ± 1.8 cm², while that of the other 12 dogs was 13.9 ± 0.7 cm², showing no differences between the two groups.

RCPA in the 0.1 mg/kg group was 77.9% (mean) one week after initiation of administration, and the area was maintained almost at this same value thereafter, showing a mean value of 71.5% after three months. Then, the rate increased to a mean value of 85.2% after four months. In the 0.2 mg/kg group, RCPA was 70.5% one week after initiation of administration. Then, the rate slightly increased to a mean value of 77.3% after two months, and the rate was maintained at almost this same value after four months. In the 0.5 mg/kg group, RCPA one week after initiation of administration was 63.4%. The rate increased after one month and reached a mean rate of 77.2% after four months. In the 1.0 mg/kg group, RCPA one week after initiation of administration was 58.3%. The mean rate was 58.7% after two months, and then, gradually increased to 75.0% after four months. In the control group, the prostatic area did not change. Thus, a 70% or higher RCPA was observed until one month after initiation of administration in the osaterone acetate 0.2–1.0 mg/kg groups, but the prostatic hypertrophy progressed gradually thereafter, and the rate after four months was approximately 75% in these three groups. RCPA caused by osaterone acetate administration showed a dose-dependent relationship.

Peripheral blood osaterone acetate, LH, and testosterone levels: Changes in the peripheral blood osaterone acetate, LH, and testosterone levels after administration of osaterone

![Graph](Fig. 1. Changes in the mean (± S.E.) prostatic area in dogs with prostatic hypertrophy after oral administration with osaterone acetate 0.1–1.0 mg/kg/day daily for 7 days.)
acetate are shown in Fig. 2, Fig. 3, and Fig. 4, respectively.

The peripheral blood osaterone acetate level peaked one week after initiation of administration in all groups, and the mean values were 36.7 ± 5.5, 70.0 ± 3.9, 144.1 ± 9.1, and 207.2 ± 22.5 ng/ml in the 0.1, 0.2, 0.5, and 1.0 mg/kg groups, respectively. Then, the mean osaterone acetate levels decreased to 12.2 ± 5.13, 36.7 ± 6.5, 65.9 ± 12.8, and 101.7 ± 33.8 ng/ml two weeks after initiation of administration, respectively, and the levels returned to the basal level after two months.

The peripheral blood LH level ranged from 0.66 to 2.01 ng/ml in each group prior to administration. After administration, the level transiently increased to approximately 4 ng/ml in the 1 mg/kg group, but no major changes were observed thereafter.

The peripheral blood testosterone level decreased after administration in the two highest dose groups, but the level stabilized after two months and thereafter.

General condition: No abnormalities were observed during the experimental period. In five of six dogs with BPH that received osaterone acetate administration, hematuria was improved within a week after initiation of administration.
in three dogs in the 1.0 mg/kg and 0.2 mg/kg groups. In two dogs in the 0.1 mg/kg group, hematuria was observed until two months after initiation of administration, then disappeared.

This study showed that canine BPH could be regressed during the early stage by oral administration of osaterone acetate. Furthermore, clinical symptoms of BPH were also improved early by administering osaterone acetate at 0.2 mg/kg or higher. In the 0.2 mg/kg or higher groups, RCPA was 70% or better one week after initiation of administration, which may have resulted in early improvement of clinical symptoms in dogs with BPH. However, dogs with BPH administered 0.1 mg/kg took a prolonged period to show improvement in clinical symptoms, which may be because RCPA remained at 80% one week after the initiation of administration. Therefore, prostatic regression to 70% may be used as an index of improvement of clinical symptoms, which was also suggested by the clinical results of our previous study using CMA [8–10].

Because prostatic regression caused by administration of osaterone acetate occurred early and sharply, this regression may be caused by direct effect on the prostate, just as in the effect of CMA [17]. Although inhibition of the upper organs was assumed as an indirect effect, decreases in the plasma LH level after administration of osaterone acetate were not clear in this study, suggesting that inhibition of the upper organs was weak. The prostatic regression by this drug persisted for approximately three months at all doses, and the prostatic hypertrophy then gradually progressed to approximately 75% after four months. This prostatic regression effect was higher than that induced by two-week administration of 2 mg/kg/day CMA observed in our previous study [13].

To discuss sizes of the canine prostate, the prostatic volume is usually obtained [5, 8–10, 19]. To obtain accurate volumes of the prostate, there are two methods, computed tomography, which we previously reported [13, 17], and transrectal ultrasonography [18]. However, these methods are performed under general anesthesia and clinical application is difficult. Generally, L, width (W), and H of the prostate are measured by X-ray or ultrasonography, and the prostatic volume is evaluated by the oval volume. In 1998, Ruel et al. observed prostatic development by ultrasonography using dogs aged 2–12 years [15]. According to their study, the relationship between the W and H of the prostate is not related to age in dogs with a similar body size to those used in this study, and the ratio is almost constant, 80.4–81.1% (mean: 80.7 ± 0.1%). Therefore, the evaluation of the prostate in this study may be the same as evaluation by volume.

REFERENCES