Effects of Oral Administration of Chlormadinone Acetate on Canine Prostatic Hypertrophy

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(Received 11 November 1992/Accepted 16 April 1993)

ABSTRACT. Seven of the 25 dogs (4 to 15 years old) with benign prostatic hypertrophy (BPH) at the teaching hospital of Nippon Veterinary and Animal Science University from 1989 through 1990 were treated orally with chlormadinone acetate (CMA), a synthetic anti-androgen, 2 mg/kg/day, twice a day for 3 or 4 weeks. Prostatic size was measured by radiography and ultrasonography before and after CMA treatment, and prostatic volume was calculated from the images. Semen quality was examined in 3 of the dogs with BPH. Peripheral blood samples were collected and plasma levels of LH, 4-androstenedione, 5a-dihydrotestosterone, testosterone and estradiol-17β were measured. Clinical signs disappeared within 10 days after the start of CMA treatment. The mean (±S.E.) prostatic volume 3 or 4 weeks after treatment decreased to 39 ± 4% of the pretreatment volume. The mean level of plasma testosterone in the dogs with BPH before treatment was significantly lower than that in the normal dogs (P<0.01). In 6 of the CMA-treated dogs the levels of all hormones examined, except LH, were significantly lower after CMA treatment than before (P<0.05). The sperm count and motility decreased and the percentage of abnormal sperms increased after CMA treatment. These results demonstrate that, although CMA treatment in dogs with BPH inhibits testicular function, the prostatic volume is markedly reduced and clinical signs disappear in a short period after the therapy. However, a relapse of BPH was observed approximately 6 months after oral CMA treatment in some dogs.—KEY WORDS: canine, chlormadinone acetate, prostatic hypertrophy.


Benign prostatic hypertrophy (BPH) is known to occur chiefly in dogs more than 4 years old [2, 25, 26]. The principal clinical signs of BPH consist of hematuria, diarrhea, rectal obstruction and dysuria [4]. It has been reported that the prostatic concentration of 5α-dihydrotestosterone (DHT) in dogs with BPH is higher than that in normal dogs, suggesting that DHT accumulation may cause BPH [7, 9, 12, 20, 28]. DHT accumulates in the canine prostate as a result of conversion of testosterone (T) secreted by the testes [8, 10]. Ito et al. [13] reported that chlormadinone acetate (CMA), an anti-androgen, inhibits T uptake and DHT formation from T in the rat prostate. Usui et al. [31] reported that plasma levels of DHT and T and the weight of the testes and the prostate of normal Beagles decrease markedly during long-term administration of CMA. Murakoshi et al. [21] observed marked atrophy of the glandular epithelium of hypertrophic canine prostates in response to CMA treatment. However, there have been no reports on the effects of CMA treatment in aged dogs with spontaneous BPH. We examined here the effects of oral CMA administration to older dogs (over 4 years old) having clinical signs of spontaneous BPH.

MATERIALS AND METHODS

Twenty five dogs (4 to 15 years old) were diagnosed as having BPH at the teaching hospital of Nippon Veterinary and Animal Science University from 1989 through 1990 based not only on hypertrophy of the prostate but on the clinical signs described by O'Shea [4]. Seven of these dogs (two Beagles, two mongrels, one Maltese, one Shetland sheep dog and one English Pointer) were treated with oral administration of CMA 2 mg/kg/day, twice a day for 3 or 4 weeks. Prostatic size was measured by radiography and ultrasonography before and after CMA treatment, and prostatic volume was calculated according to the formula, 4/3π · length · width · depth · 1/8, as described by Tunn et al. [30].

Peripheral plasma samples were collected from the cephalic vein of the 25 dogs with BPH and 4 normal dogs (5 to 7 years old), and plasma levels of LH, 4-androstenedione (A), DHT and estradiol-17β (E2) were measured. A single blood sample was taken from all the dogs with BPH. In the normal dogs, however, samples were collected four times at 3 hour intervals, and the mean level of each plasma hormone was calculated. In 6 of the 7 CMA-treated dogs a single blood sample was also taken after the treatment.

Plasma LH was measured by means of a double-antibody radioimmunoassay in accordance with the procedure described by Nett et al. [23], except that radiolabeled porcine LH (LER-778) and anti-porcine LH serum were utilized as reported previously [14]. Purified canine LH (LER-1685) was used as the standard. Plasma levels of A, DHT, T and E2 were determined by radioimmunoassay according to previous reports [14, 15].

Semen specimens were collected from 3 of the 7 CMA-treated dogs by digital manipulation before and after treatment. Each specimen was examined for the total number of sperms, motility, viability and percentage of abnormal sperms using the methods described previously [16].
RESULTS

Radiography revealed a severely enlarged prostate in the caudal abdomen of all of the dogs with BPH (Fig. 1-A). A few cysts in the parenchyma of the prostate were detected by ultrasonography in the dogs with hematuria (Fig. 1-B). Prostatic volume of the 2 dogs examined one week after CMA treatment had decreased to 49% and 59% of pretreatment volume, respectively, and the mean (± S.E.) percentage volume in all the 7 dogs treated CMA was 39 ± 4% 3 or 4 weeks after the treatment (Figs. 2 and 3). The clinical signs of BPH disappeared from all the dogs within 10 days after the start of CMA treatment. Since 2 of the 7 dogs had the relapses of BPH with clinical signs approximately 6 months after treatment, the same therapy was repeated. In the remaining 5 dogs, however, no
Table 1. Plasma levels (mean±S.E.) of LH, 4-androstenedione (A), 5α-dihydrotestosterone (DHT), testosterone (T), and estradiol-17β (E₂) in 25 dogs with benign prostatic hypertrophy (BPH) before CMA treatment and 4 normal dogs

<table>
<thead>
<tr>
<th></th>
<th>LH (ng/ml)</th>
<th>A (ng/ml)</th>
<th>DHT (ng/ml)</th>
<th>T (ng/ml)</th>
<th>E₂ (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs with BPH</td>
<td>7.38±1.05</td>
<td>0.47±0.12</td>
<td>0.21±0.04</td>
<td>1.36±0.32</td>
<td>17.92±3.23</td>
</tr>
<tr>
<td>Normal dogs</td>
<td>6.05±0.38</td>
<td>0.31±0.04</td>
<td>0.30±0.04</td>
<td>2.83±0.38</td>
<td>15.75±1.45</td>
</tr>
</tbody>
</table>

a) Significantly different from the normal dogs (P<0.01).

Fig. 4. Changes of plasma levels of LH, 4-androstenedione (A), 5α-dihydrotestosterone (DHT), testosterone (T), and estradiol-17β (E₂) in 6 dogs with benign prostatic hypertrophy before and after CMA treatment. The levels of plasma hormones in most dogs fall after the therapy.

relapses were observed during the entire year after treatment.

The plasma hormone levels of the 25 dogs with BPH and 4 normal dogs are shown in Table 1. The mean plasma T level in the dogs with BPH before treatment was significantly lower than that in normal dogs (P<0.01). Changes in the plasma hormone levels of the 6 dogs before and after CMA treatment are shown in Fig. 4. The mean (± S.E.) hormone levels before and after the treatment were 7.78 ± 1.43 ng/ml and 6.62 ± 1.21 ng/ml in LH, 0.80 ± 0.12 ng/ml and 0.30 ± 0.04 ng/ml in A, 0.25 ± 0.03 ng/ml and 0.13 ± 0.02 ng/ml in DHT, 1.62 ± 0.39 ng/ml and 0.68 ± 0.16 ng/ml in T, and 20.50 ± 4.00 pg/ml and 7.33 ± 0.07 pg/ml in E₂, respectively. Except LH, all the hormone levels were significantly lower after CMA treatment than before (P<0.05).

The semen quality of the 3 dogs with BPH is shown in Fig. 5. The number, motility and viability of sperms of all of the dogs decreased markedly, and the percentage of abnormal sperms increased after CMA treatment.

Fig. 5. Changes of the number, motility, and viability of sperms, and percentages of abnormal sperms in the 3 dogs with benign prostatic hypertrophy before and after CMA treatment. Semen quality becomes worse after the therapy.

There have been many studies concerning the effects of anti-androgens on experimentally induced canine BPH [21, 24, 29–31]. However, little information has been available on spontaneous BPH in aged dogs [3, 22]. Usui et al. [31] observed that the plasma levels of DHT and T and weight of the testes and the prostate of normal Beagles aged 7–9 months decreased markedly after oral administration of CMA of 20 mg/kg/day for 3 months. Murakoshi et al. [21] observed that oral treatment with CMA, 2.5 mg/kg/day for 3 weeks caused marked atrophy of the glandular epithelium of the prostate in dogs with BPH. In the present study, oral treatment of CMA of 2 mg/kg/day reduced the prostatic volume in BPH to less than 50% of the pretreatment level within 3 or 4 weeks after treatment and resulted in the resolution of clinical signs within 10 days after the start of CMA treatment. Ito et al. [13] reported that CMA inhibits the uptake of T and the formation of DHT from T in the prostate. In this study, the levels of all the plasma hormones in many dogs with BPH, except T, were not different from those in normal dogs and there was no marked change in the plasma level of LH in response to CMA treatment. However, the levels of A, DHT, T and E₂ in all of the dogs with BPH remarkably fell after CMA treatment. Moreover, semen quality deteriorated as a result of CMA.

DISCUSSION
treatment. It was considered that these resulted from a decline of production of steroid hormones in the testis. It was therefore proved that CMA directly inhibits endocrine function of the testis in the dog as well as in the rat [13]. Not only anti-androgen effects of CMA to the prostate but also a decline in the androgen secretory function of the testis caused by the treatment may be also related to atrophy of the hypertrophic prostate.

Brendler et al. [2] and Cochran et al. [5] found that the plasma T levels of dogs decrease with advancing age. It has been reported that there are no differences between the levels of plasma T [18] and E2 [2] in dogs with BPH and those in normal dogs. Cochran et al. [5] and Lloyd et al. [18], however, reported that plasma E2 levels in dogs with BPH are higher than those in normal dogs. Injections of E2 plus DHT or 3α-androstanediol are generally administered to induce experimental BPH in dogs [1, 5, 6, 30]. Moore et al. [19] found that E2 enhances activity of DHT receptors in the prostate and causes BPH in the dog. Schulze and Barrack [27] reported that estrogen receptors are contained in the glandular epithelium of the hypertrophic prostate of the aged dogs but not in the epithelium of the normal prostate of young dogs. Brendler et al. [2] noted that the development of BPH in the dog is associated with altered sensitivity of the prostate to plasma androgen or a response of the prostate to a relative decrease in plasma androgen to estrogen ratio. In this study, however, there was no significant difference between the mean levels of plasma E2 in the dogs with BPH and the levels in the normal dogs, and the mean level of plasma T in the dogs with BPH was significantly lower than that in the normal dogs. These findings suggest that the development of canine BPH is related to the decrease in plasma T/E2 ratio accompanying aging.

In the present study, there was no significant difference between the mean levels of plasma DHT in the dogs with BPH and the levels in the normal dogs. However, it has been reported that in dogs the DHT content of the hypertrophic prostate is higher than that of the normal prostate [9, 12, 18, 20, 28]. Issacs and Coffey [12] found that in canine BPH there are marked increases in the activity of prostatic enzymes which produce DHT. Hammond [11] stated that DHT accumulation in the human hypertrophic prostate results from decreased conversion of DHT to 3α-androstanediol. Ito et al. [13] reported that CMA inhibits the formation of DHT from T in the rat prostate. The effects of CMA treatment on canine BPH may therefore be caused by inhibiting DHT accumulation in the prostate and by decreasing production of androgens and estrogens in the testis.

Kimura and Higuchi [17] observed a relapse of human BPH approximately one year after CMA therapy. In this study, BPH reoccurred in 2 of the 7 dogs treated with CMA within 6 months after the therapy. It is therefore necessary to be aware of some possibility of a relapse of BPH occurring approximately 6 months after the completion of CMA therapy in the dog.

REFERENCES


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