Effects of a New Non-Steroidal 5α-Reductase Inhibitor, FK143, on the Prostate Gland in Beagle Dogs

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Received January 17, 1997 Accepted March 18, 1997

ABSTRACT—FK143 (4-[-3-[-bis(4-isobutylphenyl)methylamino]benzoyl]-1H-indol-1-yl]-butyric acid) is a new non-steroidal inhibitor of steroid 5α-reductase (5α-reductase). The effects of FK143 on prostate size and histopathology of mature male beagle dogs were investigated and compared with those of finasteride (a steroidal 5α-reductase inhibitor), and allylestrenol and chlormadinone acetate (CMA) (androgen receptor antagonists). FK143 was orally administered to the dogs daily for 12 weeks. At doses of 10 and 32 mg/kg, FK143 significantly reduced prostate volume to about 60% of the initial value, and dogs treated with FK143 showed a dose-dependent glandular epithelial atrophy in the prostate. FK143 showed no abnormal changes in organ weights and histopathology of the adrenal, testis, pituitary and liver. The degree of prostate reduction in the dogs treated with FK143 (10 and 32 mg/kg) was almost the same as that by finasteride (1.0 mg/kg) and smaller than that by allylestrenol (10 mg/kg) or CMA (10 mg/kg). However, allylestrenol increased liver weights, and CMA increased liver and reduced adrenal weights. These results demonstrate that FK143 can decrease the volume of the dog prostate without any influence on other organs, and they suggest that FK143 is a good candidate for the treatment for benign prostatic hyperplasia.

Keywords: FK143, 5α-Reductase, Benign prostatic hyperplasia

Progressive enlargement of the prostate gland is a common finding in patients with benign prostatic hyperplasia (BPH). It leads to pressure on the urethrae because the urethrae is anatomically surrounded by the prostate. Patients with BPH often complain of urinary problems. While the pathogenesis of BPH remains undefined, recent evidence suggests that dihydrotestosterone (DHT), which is the more active androgen and is formed from testosterone by steroid 5α-reductase (5α-reductase), plays a crucial role in BPH (1–4). Many androgen receptor antagonists, which block DHT binding to androgen receptor, have been developed and proven to be highly effective against BPH. However, the clinical use of androgen receptor antagonists has been limited because they show adverse effects such as reduction of libido and hepatic toxicity, which are respectively due to androgen deprivation and the steroidal structure of the antagonists (5).

Since the concentration of DHT in the hyperplastic prostate of humans and dogs is higher than that in the normal prostate, and men with a genetic deficiency in 5α-reductase activity have small prostate glands (6, 7), 5α-Reductase inhibitor was expected to reduce enlarged prostate and improve urinary problems (8, 9). 5α-Reductase inhibitors such as finasteride have recently been developed. Clinical studies with finasteride have demonstrated a reduction of prostatic volume, an increase in urinary flow rate and an overall improvement in symptoms without any adverse effects (10–12). Therefore 5α-reductase inhibitors have been recognized as promising therapies for BPH.

FK143, 4-[-3-[-bis(4-isobutylphenyl)methylamino]benzoyl]-1H-indol-1-yl]-butyric acid, is a newly synthesized non-steroidal 5α-reductase inhibitor. Our previous studies demonstrated that FK143 inhibits 5α-reductase in a non-competitive fashion (13). In an in vitro assay, FK143 inhibited human, dog, monkey and rat prostatic 5α-reductase with an IC50 value almost the same as that of finasteride. In an in vivo study, FK143 reduced the weight of the prostate and the intraprostatic concentration of DHT in rats (14).

Dogs are known to frequently develop spontaneous BPH with aging (15) or be amenable to experimental induction of BPH by steroidal treatment (16). For this reason, the dog is considered to be a good model for
evaluating the efficacy of a drug for human BPH. In the present study, we investigated the long term effects of FK143 on the prostate volume of mature beagle dogs and found that FK143 is effective in reducing the prostate volume without any adverse effects.

MATERIALS AND METHODS

Chemicals
FK143 and finasteride were synthesized, and allylestrenol was extracted from commercially available tablets at the Research Laboratories of Fujisawa Pharmaceutical Co., Ltd. (Osaka). Chlormadinone acetate (CMA), tris(hydroxymethyl)aminomethane (Tris), triamcinolone acetonide, α1-antitrypsin and leupeptin were purchased from Sigma (St. Louis, MO, USA). DHT, ethylenediaminetetraacetate disodium salt (EDTA), sodium molybdate (Na2MoO4), dimethyl sulfoxide (DMSO), Norit A, glycerol and dithiothreitol were from Nacalai Tesque (Kyoto). Dextran T-70 were from Pharmacia (Uppsala, Sweden). 17α-Methyl-[3H]mibolerone (specific activity 2967.4 Gbq/mmol) and Aquasol-2 were from New England Nuclear (Boston, MA, USA).

Animals
Mature male beagle dogs (3–8-years-old) were purchased from the Imamichi Institute for Animal Reproduction (Tsuchiura) and the Ohito Biotec Center, Inc. (Shizuoka). They were housed in a controlled environment. They were fed commercially available chow.

Drug treatment
Mature male beagle dogs were acclimated for 3 weeks. The treatment groups were intact control, castrated control, FK143 (3.2, 10 and 32 mg/kg), finasteride (1.0 mg/kg), allylestrenol (10 mg/kg) and CMA (10 mg/kg). Each group consisted of four males. All the drugs were given orally. The control capsules, FK143 and CMA were administered for 12 weeks, and finasteride and allylestrenol were administered for 9 weeks. For comparison, four dogs were castrated at the start of drug treatment, and these animals were the castrated control group. The drugs were administered in gelatin capsules, while the control dogs and castrated dogs received empty capsules.

Estimation of prostate volume by transrectal ultrasonography
Prostatic volumes of the dogs were determined by transrectal ultrasonography every 3 weeks after the first treatment. Ultrasound measurement of the canine prostate was performed with a Sonolayer SSA-250A Ultrasound Imager (Toshiba, Tokyo). Before transrectal measurement, the rectum was cleared of feces by enema to permit accurate imaging of the prostate. Following anesthetization, the dogs were placed in a prone position on an animal operating table. The Toshiba transrectal probe (PVL-516s, 5 MHz) was lubricated and passed into the rectum. A condom was used to cover the probe and was inflated with water to improve the image, of which the transaxial area was calculated by an internal computer. The transaxial areas of the total prostate were measured at intervals of 3 mm by moving the transrectal probe from one end to the other. The volume of each 3 mm slice was calculated and the total prostatic volume was calculated from the sum of these areas.

Necropsy
Two days after the last dosing, the dogs were sacrificed by exsanguination under deep anesthesia with an intravenously administered barbiturate. As part of the histological examination, the prostate, adrenal, testis, pituitary and liver were removed and weighed.

Histopathological examination
The prostate, adrenal, testis, pituitary and liver were fixed in 10% neutral-buffered formalin. They were embedded in paraffin, mounted and stained with hematoxylin and eosin. We graded the severity of hypertrophy in the case of the FK143 treated groups as follows: −, same as the castrated group; +, slight; ++, moderate; and +++, marked.

Binding assay for the androgen receptor of dog prostatic cytosol
Binding of drug to the cytoplasmic androgen receptor of the dog prostate was determined by standard dextrancoated charcoal (DCC) adsorption techniques (17). The dog prostate was removed and immediately frozen. Before the experiment, the prostate was thawed and washed with ice cold buffer (10 mM Tris-HCl buffer pH 7.4, 1 mM EDTA, 10 mM sodium molybdate, 10% (v/v) glycerol, 5 mM dithiothreitol, 25 μg/ml of α1-antitrypsin and 25 μg/ml of leupeptin). All the following procedures were performed at 4°C. The prostate was homogenized in the buffer (12 ml/prostate 7.2 g) with a Polytron Homogenizer, and the homogenate was centrifuged at 108,000 × g for 1 hr. The resulting supernatant was used as the source of cytosolic androgen receptor and stored at −80°C until use.

Ten-microliter samples of FK143, DHT and CMA dissolved in DMSO or a DMSO control were incubated with 100 μl of dog prostatic cytosol and 100 μl of 17α-methyl-[3H]mibolerone (diluted with assay buffer to the final concentration of 10 nM) at 4°C for 16 hr. The assay buffer contained 10 μM triamcinolone acetonide so as to inhibit binding of the radioactive ligand to progesterone and...
glucocorticoid receptors. The bound and free ligand were
separated by adding 200 μl of DCC suspension (contain-
ing 0.5% activated charcoal and 0.05% Dextran T-70 in
the buffer). After further incubation for 10 min at 4°C,
the tubes were centrifuged at 1,500 × g for 5 min. A 100-μl
aliquot of the supernatant was suspended in 5 ml of
Aquasol-2 and counted with a scintillation counter.

Statistical analyses
Analysis of variance was performed, and the paired t-
test or Dunnett’s t-test was used to determine significance
of differences.

RESULTS

Effects on dog prostate volume measured by ultrasonography

Mature beagle dogs were orally administered with
FK143 daily for 12 consecutive weeks at doses of 3.2, 10
or 32 mg/kg. Prostate volume was measured by
ultrasonography at 3, 6, 9 and 12 weeks after the first
drug treatment. Figure 1A shows that the prostatic
volume of the control dogs remained almost constant
throughout the experiment. FK143 significantly and dose-
dependently reduced the volumes of the prostate. In the
dogs treated with FK143 at doses of 10 and 32 mg/kg, a
reduction in the prostate volume was observed 3 weeks
after the first treatment, and the greatest reduction (about
60% of the initial volume) was between 9 and 12 weeks.
As compared with the initial volumes, the inhibitory
effects of FK143 at doses of 10 and 32 mg/kg were sig-
nificant at 9 and 12 weeks and at 3, 6, 9, 12 weeks after
the first treatment, respectively. Treatment with FK143 at
a dose of 3.2 mg/kg did not show any effect on prostate
reduction. In the castrated dogs, a more than 80%
decrease in the prostate volume was observed, when
compared to the initial values.

CMA was administered at a dose of 10 mg/kg for 12
weeks. Figure 1A shows that CMA decreased the prostate
volume to about 30% of the initial value. The effects of
FK143, CMA and castration on the prostate volume were
observed 3 weeks after the first administration with the
strongest increase at 9 weeks, and a slight reduction was
observed at 12 weeks. Therefore, in subsequent experi-
ments, the drugs were given for 9 weeks; finasteride was
given at a dose of 1.0 mg/kg and allylestrenol was given
at a dose of 10 mg/kg. Figure 1B shows that with
finasteride, prostate volume was reduced to about 60% of
the initial volume after 6 weeks. There was one accidental
death on week 9. With allylestrenol at a dose of 10
mg/kg, the prostate was reduced to about 40% of
the initial value after 9 weeks. Finasteride had almost
the same effect on the prostate volume as FK143. CMA and
allylestrenol showed higher efficacy than FK143.

Effects on organ weights in dogs

Two days after the last dosing, the dogs were weighed
and sacrificed. The organs were removed as part of the
necropsy and weighed. FK143 dose dependently reduced
the weight of the prostate to 99%, 84% and 72% of the
control prostate weight at doses of 3.2, 10 and 32 mg/kg,
respectively (Table 1). These values corresponded well to
the prostate volumes estimated by ultrasound measure-
ment. Administration of FK143 had no effect on body

Fig. 1. Effects of FK143, CMA, finasteride and allylestrenol on prostatic volume in beagle dogs. A: Dogs were orally ad-
ministered with drugs for 12 weeks. Prostate volumes of the dogs were measured 3, 6, 9 and 12 weeks after the first
treatment. Animal groups are as follows: ● control; ○ FK143, 3.2 mg/kg; △ FK143, 10 mg/kg; □ FK143, 32 mg/kg; ○ CMA, 10
mg/kg; ■ castrated control. Each value represents the mean ± S.E. *P<0.05, **P<0.01, compared with the initial value (paired
t-test). B: Dogs were orally administered with drugs for 9 weeks. Prostate volumes of the dogs were measured 3, 6 and 9 weeks
after the first treatment. Animal groups are as follows: ● control; ○ finasteride, 1.0 mg/kg; △ allylestrenol, 10 mg/kg. Each
value represents the mean ± S.E. *P<0.05, **P<0.01, compared with the initial value (paired t-test).
weight or the weights of the adrenal, testis, pituitary and liver when compared to the control weights (Table 1). CMA at a dose of 10 mg/kg decreased the weights of the prostate to 33% of the control. It also significantly decreased the weights of the adrenal, and significantly increased the weights of the liver, but showed no effect on the other organs (Table 1). Finasteride at a dose of 1.0 mg/kg reduced the weights of the prostate to 69% of the initial weight and significantly increased the weight of the testis, but had no effect on the other organs (Table 2). Significant reductions of the weights of the prostate to 49% of the control and hypertrophy of the liver were observed in the allylestrenol-treated dogs (Table 3). There was no effect on other organs.

**Histology of the prostate**

Representative light microscopic features are shown in Fig. 2. In the control group, the glandular epithelial cells were markedly hypertrophic, and the amount of inter-acininar fibro-muscular stroma was not extensive (Fig. 2A). On the other hand, FK143 caused marked atrophy of the glandular epithelium, characterized by flattened cells with vacuolated cytoplasm (Fig. 2B). The severities of atrophy seen in the FK143-treated group and the castrated group are summarized in Table 4. Dogs treated with FK143 showed atrophy of the prostate in a dose-dependent manner: three of the 4 dogs in the 32 mg/kg of FK143 group had moderate prostate atrophy. The castrated dogs showed severe glandular epithelial atrophy. In the CMA (Fig. 2C)- and allylestrenol (data not shown)-treated groups, more severe atrophy in the glandular epithelial of the prostate was also observed, and the severity was less marked than in the castrated dogs and more marked than in the FK143-treated dogs. Finasteride treatment resulted in almost the same degree of atrophy as treatment with FK143 (data not shown). In all the groups described above, no change was observed in the stromal region of the prostate. There was no abnormal histopathology of

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**Table 1. Effects of FK143 and CMA on organ weight in male dogs**

| Drug    | Dose (mg/kg) | Body weight gain (kg) | Prostate (g) | Adrenal (mg) | Testis (g) | Pituitary (mg) | Liver (g) |
|---------|--------------|-----------------------|--------------|--------------|------------|----------------|-----------|
| Control | 0.33         | 13.5 ± 2.0*          | 1402 ± 171  | 15.6 ± 3.3   | 72 ± 3     | 291 ± 34       |
| FK143   | 3.2          | 13.3 ± 3.6           | 1730 ± 220  | 16.8 ± 1.9   | 54 ± 5     | 383 ± 53       |
|         | 10           | 11.4 ± 2.7           | 1466 ± 18   | 15.5 ± 1.4   | 77 ± 5     | 338 ± 21       |
|         | 32           | 9.7 ± 0.9            | 1308 ± 104  | 15.4 ± 2.4   | 66 ± 6     | 316 ± 29       |
| CMA     | 10           | 4.4 ± 0.6            | 774 ± 112*  | 14.4 ± 2.9   | 75 ± 3     | 541 ± 80**     |
| Castration | -0.55      | 2.5 ± 0*             | 1214 ± 86   | 58 ± 2       | 316 ± 16   |

*P<0.05, **P<0.01, vs control (Dunnett’s t-test).

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**Table 2. Effects of allylestrenol on organ weight in male dogs**

| Drug        | Dose (mg/kg) | Body weight gain (kg) | Prostate (g) | Adrenal (mg) | Testis (g) | Pituitary (mg) | Liver (g) |
|-------------|--------------|-----------------------|--------------|--------------|------------|----------------|-----------|
| Control     | 0.40         | 15.9 ± 2.4*          | 1404 ± 135   | 16.8 ± 1.1   | 69 ± 5     | 255 ± 12       |
| Allylestrenol| 10           | 7.6 ± 1.2            | 1519 ± 96    | 18.4 ± 1.5   | 77 ± 7     | 325 ± 16*      |

*P<0.05, vs control (Dunnett’s t-test).

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**Table 3. Effects of finasteride on organ weight in male dogs**

| Drug        | Dose (mg/kg) | Body weight gain (kg) | Prostate (g) | Adrenal (mg) | Testis (g) | Pituitary (mg) | Liver (g) |
|-------------|--------------|-----------------------|--------------|--------------|------------|----------------|-----------|
| Control     | 0.02         | 14.4 ± 3.0*          | 1323 ± 92    | 15.4 ± 1.5   | 56 ± 1     | 248 ± 12       |
| Finasteride | 1.0          | 9.9 ± 3.6            | 1167 ± 33    | 25.5 ± 3.7** | 72 ± 5     | 284 ± 12       |

*P<0.05, **P<0.01, vs control (Dunnett’s t-test).
the other organs in FK143-treated dogs.

**Binding assay for dog androgen receptor**

Binding affinities of the drugs for the androgen receptor in the dog prostate were investigated by the DCC method. DHT dose-dependently reduced the binding of 17α-methyl-[3H]mibolerone and completely displaced it at a concentration of $10^{-6}$ M. FK143 showed no displacement of the ligand at concentrations up to $10^{-5}$ M (Fig. 3). CMA showed a slightly lower affinity for the dog androgen receptor than DHT.

### Table 4. Effects on the prostatic hypertrophy

| Group | Dose (mg/kg) | Histological grading |
|-------|-------------|---------------------|
|       |             | -      +     ++    +++ |
| Control |            | 4      |        |      |
| FK143  | 3.2         | 1      | 3      |     |
|        | 10          | 3      | 1      |     |
|        | 32          | 3      | 1      |     |
| Castration |      | 4      |        |      |

Severity of hypertrophy: -, normal; +, slight; ++, moderate; ++++, marked.

**Fig. 2.** Representative histomorphology of the prostates from dogs treated with FK143. ×100. A: control; B: FK143, 32 mg/kg; C: CMA, 10 mg/kg.

**Fig. 3.** Binding affinity for the dog prostatic androgen receptor. Competition of non-radioactive drugs for in vitro binding of [3H]mibolerone in dog prostate was measured. DHT, FK143, CMA. Each value represents the mean ± S.E. (n = 3).
DISCUSSION

In our previous paper, we investigated the in vitro and in vivo effects of FK143 (13, 14). Although FK143 reduced the weight of the rat ventral prostate in the in vivo study (13), the rat model is not necessarily suitable for evaluating human BPH because there are differences between rats and humans such as absence of spontaneous BPH in rats (18) and differing distributions of the 5α-reductase isozymes (19–22). The dog is considered to be a better model to test the efficacy of drugs because spontaneous BPH occurs in older dogs (15) and experimental BPH can be induced by treatment with steroids (16). In this report, we described the in vivo effect of FK143 on the beagle dog prostate.

Ultrasoundography was adopted to evaluate the volume of the prostate in dogs (23). Using this method, we can evaluate the prostate volume continuously throughout the experiment. In order to improve the precision of measurement, we measured the transaxial areas of the prostate every 3 mm. This method yielded values of prostatic volume and weight that correlated well with each other and was considered to improve the accuracy of the present experiment.

As shown in Fig. 1, treatment with FK143 significantly and dose-dependently reduced volumes of the ventral prostate in mature beagle dogs. FK143 treatment at a dose of 32 mg/kg reduced the prostate volume to about 60% of the original volume after 9 weeks of treatment. We have reported that FK143 strongly inhibited dog prostatic 5α-reductase with a similar value to that in rats (IC₅₀ of 4.9 nM), and treatment with FK143 decreased the intraprostatic DHT in dogs (13, 14). Therefore, the decrease of the prostatic volume observed in the present study may be ascribed to the blockade of DHT formation in the prostate by 5α-reductase inhibition.

Finasteride at a dose of 1.0 mg/kg decreased the prostate volume to 57% of the original after 6 weeks of treatment, in good agreement with a previous report by Cohen et al. (24) that finasteride at a 1.0 mg/kg dose reduced the prostate volume to 61% of the original at 7 weeks. In the present study, FK143 showed an effect almost equal to finasteride in decreasing prostate volume. Finasteride is already used in clinics; therefore, it is suggested that FK143 would be clinically useful in a similar way.

In an in vitro assay, FK143 inhibited dog prostatic 5α-reductase with an IC₅₀ value almost the same as that of finasteride (14); however, the efficacy of FK143 in the in vivo study was less than that of finasteride. The lower bioavailability of FK143 was considered as a reason for this discrepancy between the in vitro and in vivo study.

Although a significant increase of testis weight was observed in the dog treated with finasteride, the histology of the testis is the same as that of the control (data not shown). This result may be due to the effect of the episodic variations in testicular weight. In addition, Peters and Sorkin reported that finasteride has no effects on the testis (11).

As shown in Fig. 1, allylestrenol and CMA showed stronger effects on the decrease of prostate volume than the 5α-reductase inhibitors, FK143 and finasteride. Seventy and 60% reductions in the prostate volumes were observed in the 10 mg/kg CMA- and allylestrenol-treated groups, respectively. However, it is well-known that extended treatment of allylestrenol and CMA is impossible because allylestrenol and CMA have side effects such as the reduction of libido and hepatic toxicity in clinical use (5). In fact, in the present experiment, treatment with allylestrenol resulted in hypertrophy of the liver. CMA increased the weight of the liver and decreased that of the adrenal. Considering the side effects of allylestrenol and CMA, FK143 is superior.

FK143 showed no effects on body weight gain (Table 1). Weights and histopathology of androgen-related organs such as the testis or adrenal were not affected by FK143, indicating that FK143 acts specifically on the prostate without affecting other organs. To examine whether or not the anti-androgenic effect of FK143 in dogs was ascribable to the inhibitory activity against 5α-reductase, the affinity of FK143 for the androgen receptor in the dog prostate was studied. FK143 did not have any affinity for the androgen receptor and was considered to have no adverse effects such as decreasing the libido. FK143 was shown to have no inhibitory effects on other hormonal enzymes such as 3α-hydroxysteroid oxidoreductase in our previous study (14). Furthermore, FK143 did not inhibit the uptake of testosterone into the prostate in rats (data not shown). Therefore, FK143 is considered to have a specific inhibitory effect on 5α-reductase, which accounted for its specific effect on prostate reduction.

5α-Reduction inhibited by FK143 resulted in slight upregulation of testosterone in dog prostate (13). Androgenic effect of testosterone is not so strong, because the affinity of testosterone to androgen receptor is 1/10 of that of DHT. Therefore upregulation of testosterone in the prostate by FK143 scarcely contributed to the androgenic augmentation, and it was considered to have no physiological effect in dogs. In fact, the upregulation of testosterone by finasteride had no physiological effect on humans, dogs and rats (11).

FK143 inhibits human and rat 5α-reductase in a non-competitive manner, while finasteride inhibits it in a competitive manner (13, 14). An in vitro study revealed that the inhibitory action of FK143 on 5α-reductase was
not affected by the substrate (testosterone) concentration, while the inhibitory effect of finasteride was attenuated by increasing the concentration of testosterone (14). These observations suggest that noncompetitive inhibitors of 5α-reductase could avoid the competitive effect of accumulated testosterone on the enzyme. However, lowering of the in vivo effect by finasteride was not observed in the present study. It is thought that the in vivo model differs from the in vitro model, which may be due to the short half life of finasteride in the dog. These results in the early restoration of testosterone to its original concentration. When treatment with finasteride was repeated, the concentration of testosterone was thought to be the same as that in dogs treated with FK143. Thus the kinetic difference between FK143 and finasteride may not be reflected in the in vivo study.

Histological examination in this study indicated that the decreases of the prostate volume induced by FK143, finasteride, allylestrenol and CMA were due to the atrophy of the glandular epithelium but not the stroma. In the case of human BPH, the increase of stroma is suggested to be the main cause of BPH (25). Laroque et al. reported that a 16-week treatment of finasteride at a dose of 1.0 mg/kg reduced both the glandular and the stromal compartments of the canine prostate (26). Recent quantitative observations suggest that age related morphologic changes such as increases in the glandular and stromal compartment volumes and a decrease in the epithelium compartment volume occur in older dogs (27, 28). These suggest that the differences between the prostates of normal young dogs and BPH old dogs may be attributable to the different effects of the drugs on the prostatic stroma.

In conclusion, FK143 reduced the volumes of the prostate as well as finasteride did, without any changes on other organs, unlike allylestrenol and CMA in dogs. These results suggest that FK143 would be a good candidate for the therapy of BPH.

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