ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Jun; 20 (6): 537 – 540
http://www.simm.ac.cn; www.chinainfo.gov.cn/periodical

Flutamide suppressed prostate hypertrophy in rats and mice

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KEY WORDS flutamide; prostatic hyperplasia; orchiectomy; prosthesis and implants; estradiol

ABSTRACT

AIM: To study the suppressive effect of flutamide (Flu) on benign prostate hypertrophy. **METHODS**: The effect of Flu 10, 25, and 50 mg·kg^{-1} ig on the prostate was tested in orchiectomized rats with sc testosterone daily for 30 d and in mice implanted with homologous strain fetal mouse urogenital sinus for 14 d. **RESULTS**: 1) Flu dose-dependently suppressed the weight and volume of each lobe of the prostate to about 10 % – 50 % of control. Also, the acini and height of epithelial cells atrophied. The effect was more powerful than that of estradiol (Est). 2) The weight and volume of the mouse prostate diminished in Flu-treated groups, but the dose-response relationship was seen only in volume. In this model, Est was better than Flu. **CONCLUSION**: Flu possesses the suppressive action on benign prostate hypertrophy.

INTRODUCTION

Prostate proliferation, especially the benign prostate hypertrophy (BPH), is a common disease in elderly men[1]. BPH is a focal disease, which is caused by 17 beta-estradiol acting on the mesenchymal part of gland and by dihydrotestosterone on the stromal and epithelial cells[2]. Decrease of androgen or blocking its action is beneficial to treat the disease[3]. The main treatment method used is operation or physical therapy. Drugs, by decreasing plasma testosterone concentration or blocking its action on the target receptor, are simple methods. They include using antiandrogens alone and in combination with estradiol (Est). The antiandrogens used previously, mainly the steroid, acting on many tissues, had many adverse reactions such as hirsutism and breast enlargement. Flutamide (Flu), a nonsteroid antiandrogen drug, has been tested widely in clinic on treatment of prostate cancer. This study was to test the effect of Flu on BPH.

MATERIALS AND METHODS

Drugs Flu (yellow powder, purity > 98.5 %, mp 110 ℃ – 113 ℃), produced by Pharmaceutical Factory of Shanghai Medical University, was first ground, then diluted by 0.5 % carboxymethyl cellulose.

Effects of Flu on benign prostate hypertrophy in rats Male SD rats (provided by Experimental Animal Center, Shanghai Medical University, Grade Ⅱ, Certificate № 2-22-8), after being anesthetized with ether, were castrated aseptically. The rats, recovered for 1 wk, were divided into 5 groups randomly. They were given 0.5 % CMC, Flu 10, 25, and 50 mg·kg^{-1} ig or Est (15 μg·kg^{-1}) sc daily. Meanwhile testosterone 0.5 mg was given sc to each rat. Rats were weighed every 3 d and the drug dose was adjusted according to the body weight. After 1 month, rats were killed. Seminal vesicle, ventral and dorsal lobes of the prostate were weighed. A small piece of tissues per lobe was used for histological examination and the remaining was re-weighed after dried at 80 ℃ for 24 h. The diameters of 10 acini were measured under the microscope, the mean of which was used as the acinium diameter of the sample, either was the height of epithelial cells.

Effects of Flu on mice with implantation of urogenital sinus tissue Kunming mice, 25 – 30 g (provided by Experimental Animal Center, Shanghai Medical University, Grade Ⅱ, Certificate № 2-22-2)

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Received 1998-03-09 Accepted 1998-11-17

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Jun; 20 (6)
E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

were anesthetized with ip pentobarbital 60 mg·kg^{-1}. Aseptically, 3 small pieces of urogenital sinus from 16-d-old homologous strain fetal mouse were implanted into the ventral lobe of the prostate. Resting for 3 d, mice were given 0.5 % CMC, Flu 10, 25, and 50 mg·kg^{-1} ig or sc Est 15 μg·kg^{-1} for 2 wk. The volume and weight of the prostate were measured.

Statistics Data were expressed as $\bar{x} \pm s$ and analyzed by t-test.

RESULTS

Effect of Flu on rat benign prostate hypertrophy By the end of experiment, the body weight of Flu 10 mg·kg^{-1} group was higher than that of the control group, but the other 2 groups were not. On the contrast, the value of the Est group was lower.

Flu dose-dependently decreased the wet weights of ventral and dorsal lobes of the prostate and seminal vesicle. Flu 10 mg·kg^{-1} made the weight of each lobe drop to half of the normal, and 10 % – 20 % of control for 50 mg·kg^{-1}. Est had the same effect except that it was much less active. With nearly the same degree to wet weight, the volume of each lobe was also smaller in Flu groups than that in control. Dose-response relationship was evident. The volume in the Est group did not decrease but increased. Each dose of Flu also decreased dry weight of lobes of the prostate. Est decreased it slightly ($P > 0.05$) (Tab 1).

Flu diminished the acini, but only 25 and 50 mg·kg^{-1} had effects on height of epithelial cells (Tab 2).

Prostate gland of the control group had large acini filled with secretions. But acini of treated groups contracted to a small one and the epithelial cells were, somewhat, destroyed. The connective tissue in the gland was much more than that in CMC group (Fig 1).

Mice implanted with urogenital sinus Except for the group treated with Flu 10 mg·kg^{-1}, the other 2 groups given Flu 25 and 50 mg·kg^{-1} had lower prostate weight and volume. In high doses, Flu had effects on mouse prostate implanted with tissues of urogenital sinus. The effect on prostate volume was in good linear dose-response relationship. The volume dropped to about 90 % – 65 % of the control group. The prostate weight in each group treated with Flu was about 85 % of normal without any dose-response relationship. In this model, Est 15 μg·kg^{-1} had a better effect than Flu (Tab 3).

Tab 1. Effects of flutamide on prostate of orchiectomized rat given testosterone 0.5 mg·d^{-1} sc for 30 d. $n = 12$ rats. $\bar{x} \pm s$. [a]$P > 0.05$, [c]$P < 0.01$ *vs* wet weight of CMC group. [d]$P > 0.05$, [f]$P < 0.01$ *vs* dry weight of CMC group. [g]$P > 0.05$, [i]$P < 0.01$ *vs* volume of CMC group.

Group/ mg·kg^{-1}	Dorsal lobe	Ventral lobe	Seminal vesicle
Wet weight/mg			
CMC	661 ± 102	564 ± 91	234 ± 36
Flu 10	253 ± 48[c]	189 ± 43[c]	81 ± 25[c]
Flu 25	132 ± 21[c]	101 ± 16[c]	31 ± 8[c]
Flu 50	104 ± 22[c]	67 ± 35[c]	19 ± 13[c]
Est 0.015	523 ± 85[c]	448 ± 99[c]	237 ± 22[a]
Dry weight/mg			
CMC	142 ± 23	121 ± 24	71 ± 54
Flu 10	52 ± 10[f]	36 ± 13[f]	18 ± 7[f]
Flu 25	25 ± 5[f]	22 ± 11[f]	5 ± 3[f]
Flu 50	20 ± 8[f]	10 ± 8[f]	2.7 ± 1.5[f]
Est 0.015	102 ± 65[d]	106 ± 55[d]	55 ± 16[d]
Volume/mL			
CMC	0.48 ± 0.13	0.37 ± 0.10	0.13 ± 0.05
Flu 10	0.24 ± 0.04[i]	0.18 ± 0.05[i]	0.07 ± 0.04[i]
Flu 25	0.15 ± 0.05[i]	0.103 ± 0.017[i]	0.046 ± 0.019[i]
Flu 50	0.12 ± 0.03[i]	0.086 ± 0.025[i]	0.018 ± 0.012[i]
Est 0.015	0.49 ± 0.07[g]	0.42 ± 0.08[g]	0.21 ± 0.03[i]

DISCUSSION

Prostate hypertrophy can be induced experimentally in adult mice by directly implanting either an intact fetal urogenital sinus or its mesenchyme tissue into the host ventral prostate gland[4], so does the procedure in rats[5]. The peak of DNA synthesis of the ventral prostate is at d 4, 7 – 16 and 35 of implantation. The overgrowth of the prostate required testis testosterone, but exogenous testosterone did not induce additional prostate enlargement[4]. Human benign prostate hypertrophy is a chronic disease. It progresses very slowly. So 30 d of urogenital sinus implantation was selected to emulate it. Some steroid antiandrogens had only a little effect on the prostate proliferation, but effect of castration was much better[6]. Maybe it accounts for the fact that steroid antiandrogens have the intrinsic androgen activities which stimulate the

Tab 2. Effect of flutamide on prostate acini in orchiectomized rats given sc testosterone 0.5 mg·d^{-1} for 30 d. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* CMC group.

Dose/mg·kg^{-1}	Dorsal lobe	Rats	Ventral lobe	Rats	Seminal vesicle	Rats
Acini diameter/μm						
CMC	524 ± 82	12	565 ± 157	12	690 ± 142	12
Flu 10	335 ± 49^c	12	359 ± 61^c	12	445 ± 83^c	12
Flu 25	247 ± 39^c	12	265 ± 69^c	12	272 ± 148^c	8
Flu 50	160 ± 40^c	12	249 ± 63^c	11	152 ± 33^c	7
Est 0.015	475 ± 57^a	12	486 ± 105^a	12	812 ± 205^d	12
Epithelial cells height/μm						
CMC	10.0 ± 3.5	12	17.4 ± 4.2	12	11.7 ± 0.9	12
Flu 10	8.1 ± 1.4^a	12	15.0 ± 1.2^a	12	11.6 ± 2.5^d	12
Flu 25	6.9 ± 1.7^b	12	13.1 ± 3.2^b	12	10.0 ± 1.8^c	8
Flu 50	6.5 ± 1.4^c	12	9.3 ± 2.5^c	11	10.3 ± 1.5^b	7
Est 0.015	10.8 ± 1.3^a	12	16.3 ± 2.5^d	12	14.2 ± 4.8^a	12

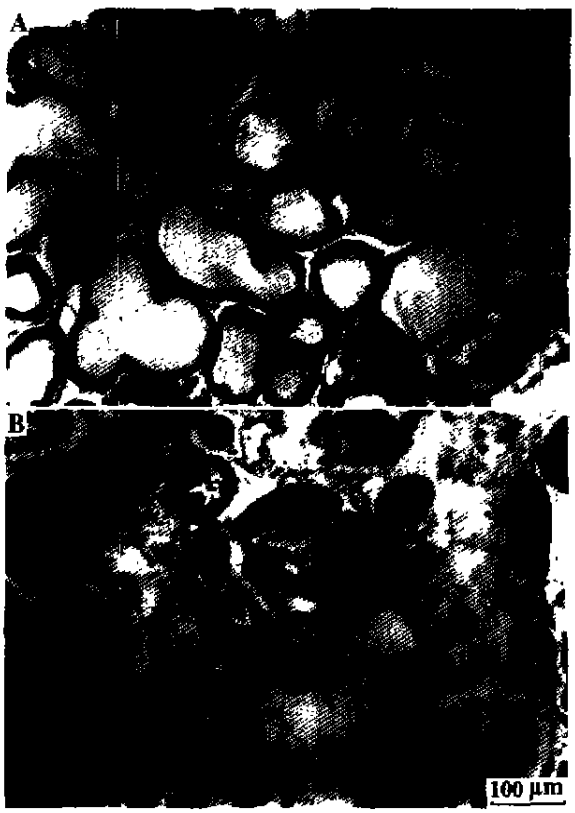

Fig 1. Dorsal lobe of rat prostate. HE stain, × 150. A) CMC group. The space between acini was small but the acini were large and without damage. B) Flu 50 mg ·kg^{-1} group. The acini were contracted, some of them were damaged. The epithelial cells were stacked. The space between acini was large and filled with connective tissues.

Tab 3. Effects of Flu on mouse prostate that were implanted with syngenic fetal urogenital sinus. $n = 12$ rats. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* CMC.

Dose/mg·kg^{-1}	Volume/mL	Wet weight/mg
CMC	0.187 ± 0.005	160 ± 24
Flu 10	0.16 ± 0.03^a	134 ± 36^a
Flu 25	0.14 ± 0.04^c	124 ± 33^b
Flu 50	0.102 ± 0.015^c	135 ± 8^b
Est 0.015	0.062 ± 0.015^c	74 ± 3^c

enlargement of the prostate. Without any androgen-like effect, Flu inhibited the enlargement of the prostate in the present study.

Flu is a nonsteroid antiandrogen. It can block the action of testosterone in target tissue and suppress the uptake of testosterone[7] without any intrinsic activity, so the enlargement of the prostate is suppressed. The results presented here confirm that. After Flu was given orally, the proliferation of the prostate caused by extra add-in testosterone was significantly lowered. The weight and volume of the prostate of rats which were given Flu 50 mg·kg^{-1} decreased to about 10 % – 20 % of normal. Flu also had a significant effect on proliferation of the mice prostate implanted urogenital sinus tissue, but this effect was not as significant as that in rats. Estradiol suppressed the rat prostate proliferation too, but it did not have any influence on the diameter of acini and the height of epithelial cells. Incontrast, Flu diminished both the acini and epithelial

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Jun; 20 (6)
E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

cell. This suggests that Flu acted on stromal and epithelial cell and estradiol acted on connective tissue. By the time suppressing the prostate proliferation, Flu did not have any influence on other tissues such as testis and adrenal[8]. The body weight did not lower but some even increased. This means that Flu is a target selective drug. After all, it can be concluded that Flu is a good drug in treatment of both prostate cancer and benign prostate hypertrophy.

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氟他胺对大鼠及小鼠前列腺肥大的抑制作用 R883 R697.310.5

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关键词 氟他胺；前列腺增生；睾丸切除术；假肢与移植；雌二醇

目的：观察氟他胺（Flu）抗前列腺肥大的作用。**方法**：以两种动物模型：阉割大鼠每只每日 sc 睾酮 0.5 mg 引起前列腺肥大和小鼠前列腺中植入同系 16 d 龄胎鼠的尿生殖窦组织，ig Flu 10、25、和 50 mg·kg^{-1} 30 d 或 sc 雌二醇(Est)，两模型分别持续 30 d 和 14 d。**结果**：1) Flu 能显著抑制大鼠各叶前列腺体积和重量，使其降至对照组的 10 %至 50 %，并呈良好的剂量效应关系。腺体上皮萎缩，腺腔直径缩小，其效应比 Est 强。2) Flu 治疗组前列腺体积和重量均减小，但只有体积项呈剂量效应关系。此模型中，Est 的作用较 Flu 强。**结论**：Flu 具有抑制前列腺肥大的作用。

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