ORIGINAL ARTICLE

Impact of Finasteride on Stroma of Benign Hyperplasia of Prostate

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Abstract:

Benign prostatic hyperplasia (BPH) is a hyperplastic process of the stromal and epithelial cells of the prostate due to effect of male sex hormone testosterone. Testosterone is the main male sex hormone, responsible for growth of sexual character and accessory sex organs. Despite its effectiveness as an male sex hormone, it causes benign prostatic hyperplasia (BPH) resulting in urinary dysfunction. On the other hand, finasteride, a 4-azastroid, inhibits the hyperplastic effect of testosterone and benign prostatic hyperplasia. The objective of the study was to observe the effects of finasteride on the stroma of testosterone induced prostatic hyperplasis in long Evans rats. This experimental study was carried out in the Department of Anatomy, Sir Salimullah Medical College, Dhaka from January to December 2006. Total 45 matured male long Evans rats of age 8-10 weeks and weighing 200-300 gm were used in this study. They were divided into three equal groups. Group A was vehicle (olive oil) control group, Group B was testosterone treated group and Group C was testosterone and finasteride treated group. The rats were sacrificed on the eleventh day. It was concluded that finasteride is an effective drug that successfully inhibits the testosterone induced prostatic hyperplasia.

Introduction:

Anatomically prostate is encapsulated with two lobes. Histologically it is a fibromusculo-branched glandular organ. It is situated on the neck of the male urinary bladder and the proximal portion of the urethra. Clinically, prostate is an important pelvic organ for its affinity to diseases like benign prostatic hyperplasia.

Testosterone is responsible for development of accessory sex organs and secondary sexual characteristics[1,2]. In the target tissue, testosterone is not the active form of the hormone, it is reduced to dihydrotestosterone (DHT) by an enzyme 5, α-reductase, which is 10 times more potent than testosterone because it dissociates from the cellular testosterone receptor more slowly[3,4,5].

In normal and abnormal prostate the growth is mediated by testosterone[6,7]. Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of prostate gland that commonly develops in the aging male. It is a hyperplastic process of the stroma and epithelial tissues of the prostate gland[8,9,10]. DHT binds to cytoplasmic receptor protein, forming a complex and then migrates to the nucleus and binds to the nuclear testosterone receptor, and induces the DNA-RNA transcription process

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which is mitogenic and leads to hyperplasia of the target organ[11,12,13].

Finasteride is a 4-azastroid, belongs to a new class of specific inhibitors of 5-α reductase[14]. Results of the study confirm that finasteride inhibit the 5-α reductase and prevent formation of DHT[15] which is responsible for hypertrophied prostate gland.

Materials and method:

Forty five adult male rats of long Evans strain weighing between 200 and 300 gm of age 8-10 weeks were used. Pure olive oil, injection testosterone propionate and injection finasteride were also used. In experimental design, rats were divided into three groups and were sacrificed on the eleventh day of study by decerebration under ether anaesthesia.

Group A: This group served as the vehicle control group and comprised of 15 rats, each rat receiving an injection of 0.2 ml of olive oil (vehicle) daily for 10 days.

Group B: This group was the testosterone control group and comprised of 15 rats, each receiving 0.32 mg testosterone propionate in 0.01 ml of suspension daily for 10 days. It showed testosterone induced prostatic hyperplasia.

Group C: This group served as the finasteride treated rats and comprised of 15 rats, and each rat received 0.32 mg testosterone propionate in 0.01 ml of suspension and finasteride 0.01 mg at 0.02 ml of suspension daily for 10 days. This group showed the effectiveness of finasteride on stroma of benign hyperplasia of prostate.

Procedure for preparing histological sections:

Out of 15 prostates in each group, histological studies were carried out on six randomly selected specimens. The ventral prostate was fixed in 10% normal saline solution and processed following the routine histological procedure. The tissues were dehydrated in ascending concentration of

Table I: Grouping of animals, doses of drugs and sacrifice schedule

Groups	Number of rats	Drug	Dose/kg/ body weight	Dose rat/day	Duration of admin-istration (in days)	Day of sacrifice (in days)
A	15	Vehicle (Olive oil)		0.2 ml	10	11
B	15	Testosterone	1.6 mg	0.32 mg at 0.01 ml	10	11
C	15	Testosterone + Finasteride	1.6 mg + 0.07 mg	0.32 mg at 0.01 ml + 0.01 mg at 0.02 ml	10	11

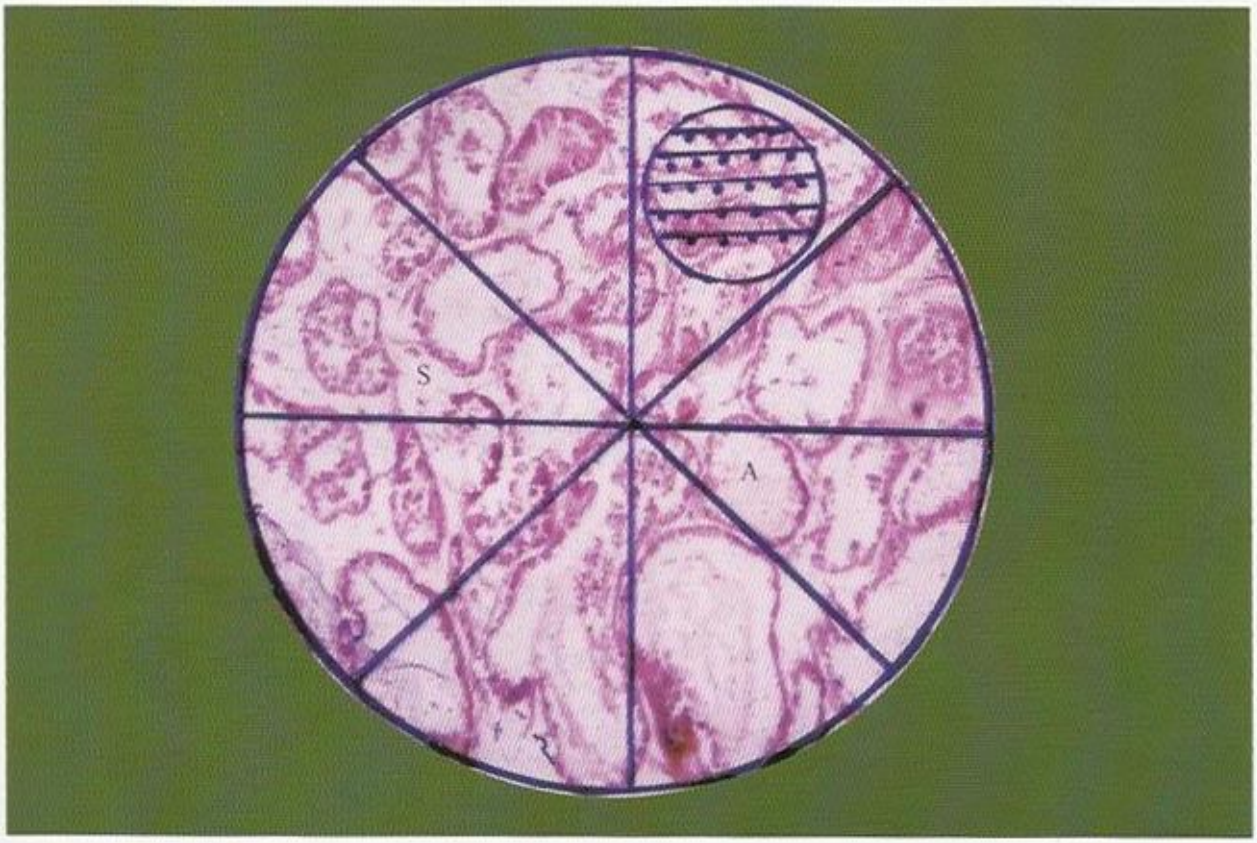

Figure-1: Photomicrograph showing procedure of measuring the percentage of stroma in prostate of rat.

alcohol, cleared in xylene, infiltrated and embedded in paraffin. Sections of the tissues of 6 µm (micrometer) thickness were made by a rotary microtome and were stained with haematoxylin and eosin (H&E). Stromal elements and muscles were stained with Van Gieson's stain.

Estimation of the stroma in the ventral prostate at low power field (X10 objectives x 10 eyepiece) of microscope:

The proportion of structural stroma of prostate were determined by using a 'Point Counting technique'. A replica of Zeiss integrating eyepiece was prepared with a transparent plastic sheet and was placed into the eyepiece. The Zeiss eyepiece contains a graticule of 25 points. Visual of the slide was divided into equal eight parts by drawing four lines on the coverslip. The counting was done under light microscope in low magnification in slides stained with routine H&E stain. At a low magnification, using an X10 objective and an X10 eyepiece, the position of each point on the graticule, falling on stroma of prostatic slide in the inter-acini space was focused. Thus, taking 25 points on the graticule for each field, a total of 200 (25x8) point positions were recorded for each slide[14].

The total number of points hitting inter-acinus prostatic stroma was summed up and expressed as a percentage of the total number of points.

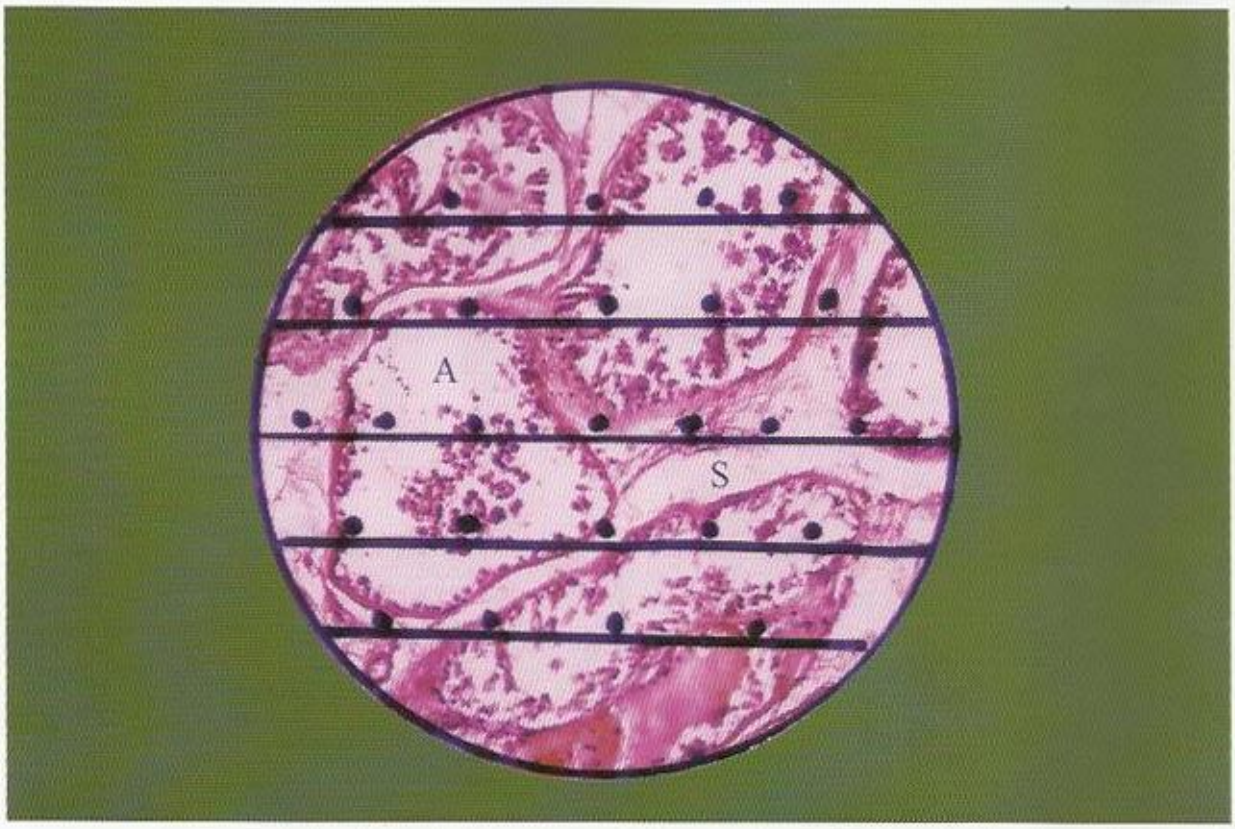

Figure-2: Photomicrograph showing procedure of estimation of the percentage of stroma in prostate of rats by Zeiss integrating eyepiece14.

Results:

Table-II and Figure-1, 2, 3 show the percentage volume of stroma between different groups of rats. The mean percentage volume of stroma in the vehicle control rats was 14.83 ± 1.78. The mean percent volume in the testosterone treated was 20.25 ± 0.69 which was higher than the vehicle treated rats. The mean percentage volume of stroma in finasteride treated groups was 15.00 ± 0.71. The value was lower than that of testosterone treated rats. The mean difference was highly significant (p<.001) when compared between the groups.

Table-II: Comparison of percentage of stroma between different groups of rats (n-6)

Groups	Stroma (%) Range	Mean ± SD
A	12.5 – 17.5	14.83 ± 1.78
B	19.0 – 21.0	20.25 ± 0.69
C	14.0 – 16.0	15.00 ± 0.71

A vs B= p<0.001 s; A vs C = p<0.50 ns; B vs C = p<0.001 s

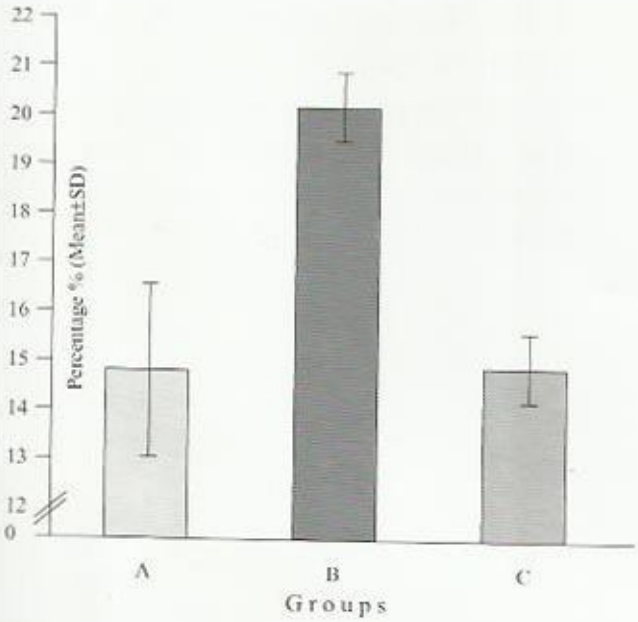

Figure-3: Percentage of stroma in different groups of rats (n=6 in each group).

Discussion:

The increases in values were due to hyperplasia of the acini and stroma of the prostate in testosterone treated rats. Shapiro et al[10] and Handlsman[12] also stated that relative increase in proportion of stroma was related to the effects of testosterone on prostate. In finasteride treated rats the percentage volume of the stroma of the prostate was lower than that of testosterone treated rats and the difference was significant ($P < 0.01$). Wilson[4] and Niu et al[9] found in their studies the same effectiveness.

Finasteride is a nonsteroidal antistestosterone used in the treatment of BPH and prostatic cancer. It effects DHT at the testosterone receptor. The trend of antitesterone effect of finasteride against testosterone induced hyperplasia is also observed in the present study.

References:

1. Bruchovsky N, Lesser B, Van Doom E, Craven S. Hormonal effects on cell proliferation in rat prostate. Vitam Horm 1975; 3: 61-102.
2. Davies P, Eaton CL. Regulation of prostate growth. J Endocrin 1991; 131: 517.
3. Doom EV, Craven S, Bruchovsky N. The relationship between androgen receptors and the hormone controlled responses of rat ventral prostate. Biochem J 1976; 160 : 11-21.
4. Guess HA. Benign prostatic hyperplasia: antecedents and natural history. Epidemiol Rev 1992; 14:131-53.
5. Handlsman DJ. Testosterone and other androgens. In: Endocrinology, Third edition. Philadelphia: WB Saunders Company, 1995. pp-2351-61.
6. Niu YJ, Mz TX, Zhang J, et al. Androgen and prostatic stroma. Asian J Androl 2003; 5: 19-26.
7. Shapiro E, Becich MJ, Hartanto MJ, Lepor H. The relative proportion of stromal and epithelial hyperlasia is related to the development of symptomatic benigh prostatic hyperplasis. J Urol 1992; 147: 1293-97.
8. Simon, W, Annemarie A, Axel A, Gerald R. Endocrinology of the prostate and benign prostatic hyperplasia. Endocrinology 2001; 4: 2357-67.
9. Waltregny D, Leau 1, Signoreti S, et al, Androgen driven prostate epithelial cell proliferation and differentiation. Mol Endocrin 2001; 15: 765-82.
10. Wilson JD, Walsh PG. Recent studies on the mechanism of action of testosterone. N Engl J Med 1996; 21: 1284-94.

11. Huttunen E, Romppanen T, Helminen HJ. A histoquantitative study on the effects of castration on the rat ventral prostate lobe. J Anat 1981; 132: 357-70.
12. Jong FH, Renvers PJ, Vreis BD, et al. Androgens and androgen receptor in prostate tissue from patients with benign prostatic hyperplasia. J Steroid Biochem Mol Biol 1992; 42: 49-55.
13. Smith RA, Wake R, Soloway MS. Benign prostatic hyperplasia. Postgrad Med 1988; 83: 79-85.
14. Elias H, Hyde DM. An elementary introduction to stereology. Physiol Rev 1980; 412-23.
15. Stoner E, and the Finasteride study Group. The clinical effects of a 5α reductase inhibitor finasteride on benign prostatic hyperplasia. J Urol 1992; 298-302.