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Castration-Like Effects on the Human Prostate of a 5α-Reductase Inhibitor, Finasteride

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Abstract Epidemiological studies strongly support the contention that surgical castration prior to age forty prevents both benign prostatic hypertrophy (BPH) and prostate cancer. 5α-Reductase deficiency in humans, an experiment of nature, is an uncommon genetically transmitted disorder in which prostate size remains very small throughout adult life. A 5α-reductase inhibitor, finasteride, has recently been shown in double-blind, placebo-controlled trails in patients with BPH to statistically decrease prostate size and improve clinical symptoms in comparison to placebo controls. In the untreated BPH prostate, tissue levels of dihydrotestosterone (DHT) and testosterone (T) averaged 4.2 and 0.2 ng/g, respectively. Following one week of finasteride therapy, T levels rose to a mean of 1.32 ng/g while DHT levels decreased to 0.62 ng/g. These values contrast with values in prostate tissue from surgical castrates in which DHT and T values average 1.14 ng/g and 0.1 ng/g, respectively. If we use the relative binding affinity of T and DHT to the androgen receptor as a criterion of biological androgen potency, T would appear to be one-fourth as potent as DHT. Using this 1:4 ratio to convert prostatic T to a biologically equivalent amount of prostatic DHT, the total biologically active DHT equivalent in the prostate following one week of finasteride averages 0.95 ng/g compared to a mean of 1.14 ng/g in surgical castrates. If the acute effects of finasteride on tissue T and DHT persist during chronic therapy, prostatic hormone concentrations could be said to closely resemble those found following surgical castration; such changes might prevent the occurrence of prostate cancer, similar to the effects noted after surgical castration in younger males.

Key words: adrenal, cancer, dihydrotestosterone, finasteride, hormone, testosterone, 5α-reductase

Castration prevents occurrence of prostate cancer. Prostate cancer has rarely, if ever, been reported in males castrated prior to age 40. Support for this thesis is best exemplified by Robert Moore who reported in 1943 [1] autopsy findings in serial sections of the prostate in patients who were castrated or hypopituitary prior to age 40, and lived into the benign prostatic hypertrophy (BPH) age group.

Moore [1] could find no histologic evidence for either BPH or carcinoma in any of these 28 prostates as compared with an expected incidence of 50% and 40%, respectively. In addition, clinical reports of a group called the Skoptzys from Russia, who have ritual castration at age 35, indicated the presence of small prostates and the rarity of prostate cancer in elders of this group [2].

Recently, finasteride, a 5α-reductase inhibitor, has been introduced as a medical treatment for BPH. This drug is a competitive inhibitor of the enzyme 5α-reductase and effectively blocks conversion of testosterone (T) as well as adrenal androgens to dihydrotestosterone (DHT), the most potent prostatic androgen [3].

Administration of 5.0 mg of finasteride daily significantly reduced prostate size, improved maximum urinary flow rates and improved clinical symptoms of BPH in a one-year, double-blind study of 895 patients with BPH [4]. Reported side effects were minimal to absent.

In addition to the clinical studies, we have measured the acute effects of 5.0 mg daily of finasteride for one week on prostate T and DHT levels. Data obtained from these studies demonstrate changes in prostatic hormone concentration following this drug that resemble those following surgical castration. This paper presents data on DHT and T levels in prostate tissue obtained from patients previously castrated for prostate cancer, and compares them to hormone levels in prostates from patients with

BPH who were treated daily with 5.0 mg of finasteride for one week prior to transurethral resection of the prostate (TURP). Implications of this comparison are also discussed.

METHODS AND MATERIALS

Clinical: Thirty-seven patients with prostate cancer who had relapsed following castration and required repeat TURP provided tissue for study of T and DHT. Nine patients with BPH who required TURP for symptomatic disease were given 5.0 mg of finasteride daily for one week prior to surgery, and T and DHT were measured in the resected tissue.

Methods: Tissue DHT was measured by a previously reported method [5]. The reagent blank for this method plus 2 S.D. was 6.0 pg. The intra-assay coefficient of variation for the DHT method was 10%. Tissue T levels were measured using an improved method for prostate androgens reported previously [5].

RESULTS

In 37 surgically castrated patients, tissue DHT averaged 1.14 ng/g, while T averaged 0.10 ng/g. In nine patients treated with finasteride, DHT averaged 0.62 ng/g and T averaged 1.32 ng/g (see Fig. 1 [3]). Tissue T and DHT values for untreated BPH and prostate cancer were 0.2 and 4.2 ng/g, respectively.

In order to compare the total biologic androgen activity in castrated and finasteride-treated prostates in a common unit, it was necessary to convert the T content of the finasteride-treated prostate to a DHT equivalent, thus allowing comparison to castrated patients whose prostatic androgen was almost totally DHT. The T, expressed as a DHT equivalent, was then added to the endogenous DHT to provide a total DHT equivalent for all treated prostates.

To establish a conversion factor for T to DHT in terms of androgenic biologic potency, we used several approaches. Wilbert and Wilson [6]

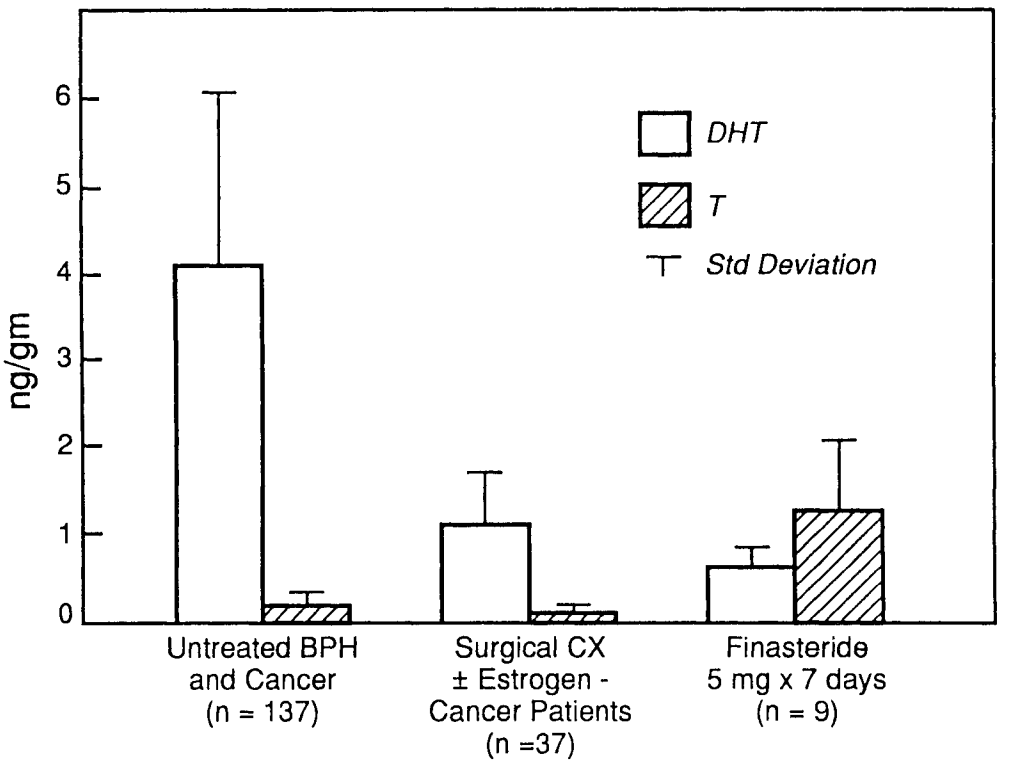

Fig. 1. DHT and T concentrations are shown in ng/g on the vertical axis. Bars depict levels of these hormones in prostates from patients with: untreated prostate cancer or BPH on the far left; prostates from previously castrated patients with prostate cancer in the center; and prostates from patients with BPH treated with finasteride, 5.0 mg daily for seven days on the right. T is indicated by the slashed bar, DHT by the open bar.

established that the DHT binding affinity to the androgen receptor was significantly greater than that of T by a factor of 4. This has been recently confirmed by Grino *et al.* [7] using the same receptor binding affinity factor. If this is in fact a valid index of biologic potency, then the mean T concentration in finasteride-treated glands of 1.32 ng/g would be equivalent to 0.33 ng/g of DHT (see Fig. 2). When this DHT equivalent is added directly to the measured DHT in finasteride-treated tissues, a total of 0.95 ng/g is noted as compared to a DHT of 1.14 ng/g in prostates of castrated patients (Fig. 2).

DISCUSSION

Since finasteride is likely to be widely used as a medical therapy for BPH it becomes important to consider its potential effects, if any, on prostate cancer. We have evaluated prostate tissue hormone concentrations in finasteride-treated patients and compared these to values found in prostates of surgical castrates. Over the past 15 years we have had the opportunity to study prostate tissue taken from 37 patients who had been previously castrated for prostate cancer. Since the mean levels of DHT in untreated prostate cancers are almost identical to those found in untreated BPH (4.2 ng/g—see Fig. 1), we felt that it was valid to compare DHT values in cancer castrates to those obtained in finasteride-treated BPH using an identical assay method. This comparison had to be done by converting tissue T to biological equivalents of DHT since T is the predominant androgen present in finasteride-treated prostates while DHT is the predominant androgen

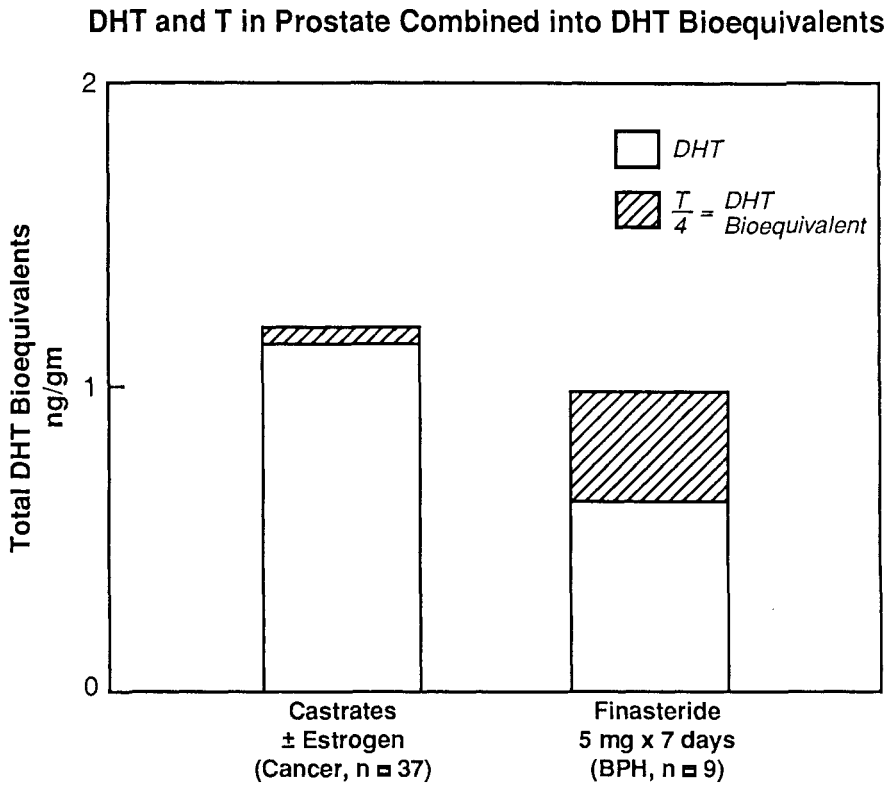

Fig. 2. Total bioequivalents of prostatic DHT are shown for previously castrated patients, on the left, and patients with BPH treated with finasteride 5.0 mg daily for seven days on the right. Endogenous DHT, directly measured, is indicated by the open bar; endogenous T concentration divided by 4 has been calculated as a bioequivalent of DHT and is shown on top of each open bar as a slashed bar. Total DHT bioequivalents for each group (endogenous DHT plus T divided by 4 in prostate tissue) are indicated in ng/g on the vertical axis.

in surgical castrates. We have used the relative binding affinity of T and DHT for the androgen receptor to convert T levels in finasteride-treated patients to DHT bioequivalents. Two published studies, one by Wilbert *et al.* [6] and one by Grino *et al.* [7] from the laboratory of Jean Wilson, show a consistent four-fold higher binding affinity of DHT for the androgen receptor as compared with T. Many studies in the literature comparing the affinity of hormone receptor binding have shown correlations of such binding to biological hormone potency [8]. When we compared total DHT bioequivalents in finasteride-treated prostates and surgically castrated prostates, as shown in Fig. 2, we found similar levels in both. Although finasteride appears to produce castration-like hormone effects in the prostate, it has few, if any, effects on male sexuality or male secondary sex characteristics. As shown in a large double-blind multicenter study of 895 patients, there was an approximate 5% incidence of impotence or loss of libido in the finasteride group compared to a 1.5% incidence of similar symptoms in the placebo-treated group over one year [4].

It must be remembered that these studies of tissue hormone levels in the finasteride-treated patients represent acute changes (7 days); it is very important to determine the long term effects of this drug on tissue hormones over months to years to see if the acute changes persist. If, in fact, these changes do persist, one might predict a decreased incidence of prostate cancer in finasteride-treated patients based on previously cited studies in castrates. The fact that prostate size, measured by MRI, remains stable in BPH patients under study for almost five years (unpublished data) suggests a sustained effect of finasteride on BPH. If and when long term study data become available, finasteride could be used in a double-blind trial in which patients under study would be those with a four-fold increased risk of prostate cancer as described by Meikle *et al.* [9] in 1982. Meikle's [9] studies dealt with men who had prostate cancer at age 62 or younger; he showed a four-fold increased risk for male siblings of the propositus. Recently Steinberg *et al.* [10] have shown that the incidence of prostate cancer is higher in patients with a strong family history, although their findings are not as specific as Meikle's.

CONCLUSIONS

1. If castration of males prior to age 40 prevents prostate cancer, then finasteride may also prevent prostate cancer. In acute studies, it produces changes in the concentration of androgenic hormones in the prostate similar to surgical castration.
2. If long term studies confirm these findings, then we suggest a trial of finasteride to prevent prostate cancer in high risk patients.

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