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Effects of Castration Compared with Total Androgen Blockade on Tissue Dihydrotestosterone (DHT) Concentration in Benign Prostatic Hyperplasia (BPH)

J. Geller and J. Albert

Mercy Hospital and Medical Center, San Diego, California, USA

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Summary. We compared the effect of a variety of drug regimens to lower prostate DHT concentration. Patients with BPH were treated for one week prior to surgery with either tamoxifen, flutamide, megestrol acetate, megestrol acetate plus tamoxifen and megestrol acetate plus DES or ketoconazole. DHT concentration in the surgically resected tissue was compared with tissues obtained from untreated patients. We also obtained prostate tissue at the time of relapse in patients with prostate cancer who had been treated with orchiectomy with or without estrogen therapy. Megestrol acetate plus the mini-dose of DES (0.1 mg) and megestrol acetate plus ketoconazole both decreased DHT concentrations in prostate tissue to levels (0.79 ng/g) significantly below those noted with orchiectomy (1.16 ng/g). The difference between the DHT concentration in the two groups (orchiectomy vs. total androgen blockade) represents the contribution of adrenal androgens to prostate tissue DHT. This small amount of DHT (approximately 0.4 ng/g) may be biologically important in stimulating prostate epithelial cell growth.

Key words: Dihydrotestosterone, Adrenal androgens, Anti-androgens, Castration, Prostate cancer.

Introduction

Dihydrotestosterone (DHT) is the major stimulus to prostate growth. It has a higher affinity for prostatic cell androgen receptor than other naturally occurring androgen metabolites or testosterone itself [8]. One of the current areas of interest and investigation in the treatment of prostate cancer is the effect of adrenal androgens on prostate tumor growth. Techniques using drugs to block both testosterone and adrenal androgens have been advocated to improve the time to progression of disease as well as survival in prostate cancer [3].

Our purpose in this study was two-fold: 1. To compare various anti-androgen therapies alone or in combination for their effect on prostate DHT concentration, since reducing DHT maximally might provide optimal suppression of hormone dependent tumor clones. 2. To compare the effect on prostate tissue DHT of orchiectomy alone to combined suppression of testicular and adrenal androgens with drug combinations such as megestrol acetate (MA) plus DES and MA plus ketoconazole. The differences in tissue DHT following gonadal suppression alone compared to total androgen ablation should provide a quantitative estimate of adrenal contribution to tissue DHT and therefore assessment of the possible biologic importance of adrenal androgens in prostate cancer.

Methods

Clinical. Patients with BPH requiring TURP for prostatic obstruction were treated for one week with one of the following regimens: tamoxifen (TM) – 20 mg twice daily po (7 patients); feulamide (FL) – 250 mg three times daily po (12 patients); megestrol acetate (MA) – 120 mg per day (23 patients); megestrol acetate 120 mg per day plus TM 20 mg twice daily (6 patients); MA 120 mg per day plus DES (E) 0.1 mg per day (4 patients); and MA 120 mg per day plus ketoconazole (KC) 400 mg 3 times daily (4 patients). Tissue was obtained for DHT concentrations; plasma for Δ_4-androstenedione and testosterone assay was also obtained just prior to surgery. Twenty-five untreated patients served as controls for this study. Tissue and plasma were also obtained from patients with prostate cancer who previously had orchiectomy but who required a TURP because of obstructive symptoms due to recurrence of their local disease.

Methods. Tissue DHT was measured by a previously reported method [1]; the reagent blank for this method plus two standard deviations was 6 picograms; the coefficient of variation for the DHT method was 10%. Plasma testosterone (T) and Δ_4-androstenedione were also measured as previously described [7].

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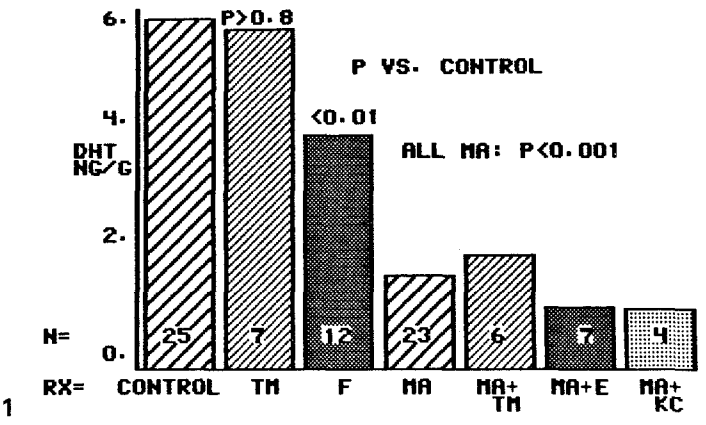

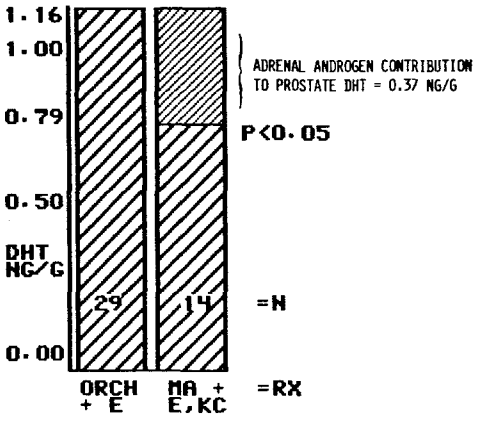

Fig. 1. Effect of hormonal blockade on prostate DHT. DHT concentration in prostate tissue is shown on the ordinate. *Bar graphs* indicate control levels of tissue DHT (far left) compared to values in patients treated with various hormonal therapies. *P* value is shown above each therapy and is statistically significant for all groups except TM (see Methods, Clinical for code to abbreviations)

Fig. 2. Prostate DHT after testicular blockade vs. total androgen ablation. DHT concentration in prostate tissue is shown on the ordinate for patients previously treated with orchiectomy with or without estrogen (*bar on left*). On the right, *thick diagonal lines* represent tissue DHT concentration following blockade of both testicular and adrenal androgens in patients treated with MA plus E and MA plus KC (combined into one group). The *thin, diagonal lines* at the top right hand bar represent DHT in prostate tissue derived from adrenal androgens. *P* value shows a significant decrease in DHT concentration in patients treated with total androgen blockade compared to orchiectomy

Table 1

RX	NG DHT/G ± SE	*N*	*P* (vs. C)	*P* (vs. MA)	*P* (vs. MA + E)	*P* (vs. MA + E, KC)
C	6.00 ± 0.45	25	1.0	< 0.001	< 0.001	< 0.001
TM	5.83 ± 0.60	7	< 0.8	< 0.001	< 0.001	< 0.001
FL	3.89 ± 0.58	12	< 0.01	< 0.001	< 0.001	< 0.001
MA	1.37 ± 0.18	23	< 0.001	1.0	< 0.05	< 0.02
MA + TM	1.77 ± 0.29	6	< 0.001	> 0.2	< 0.02	< 0.01
MA + E	0.81 ± 0.17	10	< 0.001	< 0.05	1.0	> 0.9
MA + KC	0.74 ± 0.11	4	< 0.001	< 0.01	> 0.7	> 0.7

Results

The effect of various drug regimens on tissue DHT compared to controls is shown in Fig. 1. Table 1 shows "*p*" values for DHT levels following various drug regimens in comparison to controls, to MA alone, and to MA plus DES or KC. It can be seen that all regimens except TM significantly decreased DHT concentration relative to controls; no significant differences were noted between DHT levels in four patients treated with MA plus DES and four treated with MA plus KC although values tended to be slightly lower in the latter group. Figure 2 shows the levels of DHT in orchiectomized patients at the time of relapse of prostate cancer. DHT values in this group averaged 1.16 ng/g of tissue which was significantly greater than the mean DHT of 0.79 ng/g for the combined group of MA plus DES and MA plus KC. The latter 2 groups of 4 each have been combined in Fig. 2 since the values were not significantly different. The difference between the mean value of the orchiectomized group and the combined group with total androgen blockade represents an estimate of the contribution of adrenal androgens to prostate DHT which was 0.37 ng/g.

Discussion

It can be seen that the combined drug regimens of MA plus DES and MA plus KC significantly decreased DHT levels below values obtained with orchiectomy alone. We have previously shown that MA plus DES decreases plasma T to castrate levels and decreases circulating adrenal androgens by approximately 50%. MA also has anti-androgen effects at the prostate level and competes with the prostate androgen receptor, further blocking DHT accumulation. Ketaconazole blocks both testosterone and adrenal androgen synthesis by

decreasing the enzyme C17–20 lysase [6] and preventing formation of C19 steroids from C21 steroids. The lower values of DHT in the MA plus DES and MA plus KC group compared to the orchiectomy group is due to total or near total androgen blockade by the former regimen. The difference between prostate DHT levels in total androgen blockade and castration represents the contribution of adrenal androgens to tissue DHT. The value of 0.37 ng/g obtained is probably an underestimate since androgen blockade is probably not complete. Nevertheless the biologic role of this relatively small amount of DHT, representing one-tenth to one-fifteenth of the total prostate DHT in untreated BPH prostates may be important in stimulating hormone sensitive tumor cells. Evidence to support this comes from several sources: Bartsch et al. [2] showed that in castrated rats prostate weight was significantly increased by testosterone injections equal to 1/100 of the daily production rate. Geller et al. [7] have shown a significant correlation between prostate DHT and epithelial cell protein synthesis over a ten to twelve-fold range of approximately 0.4 ng/g up to 5 ng/g, supporting the biologic importance of small amounts of DHT. Of utmost importance in supporting the role of adrenal androgens in stimulating prostate tumor growth is the fact that approximately one-third of patients in relapse following castration or DES have an additional remission with adrenal androgen blockade using drugs such as aminoglutethimide, ketoconazole, flutamide or Megace (MA) [5]. Of interest in our studies was the fact that flutamide, a pure anti-androgen that competes for the androgen receptor, lowered tissue DHT significantly compared to control but to a much lesser extent than other regimens for total androgen blockade. In endocrinologically intact patients this probably is due to a feedback increase in pituitary LH and plasma T that partially negates the effect of the drug at the dose given.

These studies establish that total androgen blockade significantly decreases prostate DHT below levels occurring with castration alone. Whether this biochemical effect is clinically important in prolonging time to progression and survival remains to be seen in the results of several clinical trials of total androgen ablation currently under study.

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J. Geller
Mercy Hospital and
Medical Center
San Diego, CA 92103
USA