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Effect of Finasteride on Adrenal Steroidogenesis in Men

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ABSTRACT: Finasteride, a 5α-reductase inhibitor, does not bind to the androgen receptor and has no other known hormonal activity. To determine what effect, if any, it has on adrenal steroidogenesis, 10 healthy men received 5 mg finasteride daily for 28 days. Adrenocorticotropic hormone (ACTH) stimulation tests were performed before and after 4 weeks of finasteride administration (5 mg daily). Serum levels of 17-hydroxypregnenolone, 17-hydroxyprogesterone, deoxycorticosterone, corticosterone, aldosterone, cortisol, dehydroepiandrosterone, and androstenedione were measured before and 60 minutes after i.v. ACTH. Finasteride decreased serum dihydrotestosterone levels from 31 ± 5 to 4.4 ± 1.2 ng/dl ($P < 0.001$). There were no significant changes in basal or ACTH-stimulated serum levels of adrenal steroids. There was also no significant decrease in the product to precursor ratio for the seven adrenal enzymes tested. Finasteride increased mean serum androstenedione levels by 17% ($P = 0.10$) and significantly increased the androstenedione to 17-hydroxyprogesterone ratio ($P = 0.02$ before ACTH and 0.05 after ACTH). These changes are most likely due to inhibition of androstenedione metabolism by 5α-reductase. In conclusion, finasteride has no detectable effect on adrenal steroidogenesis, other than that which can be explained by inhibition of the 5α-reductase enzyme.

Key words: 5α-Reductase inhibitor, androgens, dihydrotestosterone, ACTH.

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The enzyme 5α-reductase converts testosterone (T) to dihydrotestosterone (DHT), the active androgen in the skin and prostate (Anderson and Liao, 1968; Bruchovsky and Wilson, 1968). Finasteride is a 4-azasteroid T analog that inhibits 5α-reductase by competing with T for the active site on the enzyme (Rasmusson et al, 1986). Finasteride has been shown to have no intrinsic androgenic, estrogenic, or progestational agonist or antagonist activity, other than that which can be explained by 5α-reductase inhibition (Stoner, 1990). However, as a steroid hormone analog, competitive inhibition of adrenal steroidogenesis is theoretically possible. Although the effect of finasteride on adrenal steroidogenesis in man has not previously been determined, a similar 5α-reductase inhibitor (4-MA) has been shown to inhibit 3β-hydroxysteroid dehydrogenase, with a K_i of 56 nM (Brandt and Levy, 1989). The present study was designed to determine whether inhibition of adrenal steroidogenesis occurs in man at the dose of finasteride used to treat benign prostatic hyperplasia (Gormley et al, 1992).

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Materials and Methods

Subjects

Ten healthy men, aged 25 to 38, were recruited to participate in this study. All were in excellent general health (as determined by medical history, physical examination, and screening laboratory testing), took no medications known to affect hormone levels, and had no clinical or biochemical evidence of endocrine disorders. All men gave written informed consent. The protocol was approved by the Research Ethics Committee of the Camp Hill Medical Centre, Halifax, Nova Scotia.

Study Design

The protocol was an open-label study in which the 10 subjects received 5 mg finasteride daily for 28 days. Adrenal steroidogenesis was assessed by measuring steroid levels immediately before, and 60 minutes after, the i.v. administration of 250 μg synthetic adrenocorticotropic hormone (ACTH) (Cortrosyn; Organon, West Hill, Ontario). ACTH was given between 1200 and 1300 hours, 7 days before starting finasteride and on the 28th day of finasteride administration.

Hormone Assays

All steroids were measured in duplicate by radioimmunoassay (RIA). The steroids measured, the source of the antibodies, and the intraassay coefficients of variation are listed in Table 1. All samples for a given patient were measured in the same assay. Serum DHT was measured after ether extraction and celite chromatography as previously described (Rittmaster et al, 1992). For the other steroids, approximately 1,000 counts per minute (cpm)

Table 1. *Radioimmunoassays: antibodies and quality control data*

Assay	Source of antibody	Intrassay coefficient of variation	Sensitivity limit
Aldosterone	Hanning 088, National Pituitary Agency	5%	3–10 ng/dl
Androstenedione	Pantex OP/09, Santa Monica, California	10%	6–11 ng/dl
Corticosterone	Dr. P. Vecsei, Heidelberg, Germany	10%	0.03–0.08 μg/dl
Cortisol	ICN Biochemicals R2P-31, Costa Mesa, California	11%	0.05–0.10 μg/dl
Deoxycorticosterone	Dr. F. Bidlingmeir, Munich, Germany	10%	3–10 ng/dl
DHEA	Pantex OP/10	7%	5–10 ng/dl
Dihydrotestosterone	Endocrine Sciences, Tarzana, California	7%	6 ng/dl
17OH Pregnenolone	Immunocorp, Montreal, Quebec	8%	5–11 ng/dl
17OH Progesterone	Marsiella Δ11 (in house)	8%	4–10 ng/dl
Testosterone	Pantex OP/08	11%	3–8 ng/dl

of the relevant tritiated steroids were added to 1 ml serum to determine procedural recoveries during extraction and chromatography steps. The serum samples were extracted with 8 ml diethyl ether, dried with air, and resuspended in 1 ml isooctane. The extract was then chromatographed on celite microcolumns using Abraham's system 1, 2, or 3 (Abraham et al, 1972), as described in Table 2. The eluted fractions containing the purified steroids were dried under vacuum and then reconstituted in phosphate buffer for RIA.

To ensure that finasteride itself would not interfere with the RIAs, the elution profile of tritiated finasteride on the celite columns and the cross-reactivity of finasteride with each of the antibodies were determined. Finasteride coelutes primarily in the corticosterone fraction (recovery = 29 ± 10%; $n = 3$) and the cortisol fraction (recovery = 48% ± 13) (Antonian et al, 1993). The only detectable cross-reactivites were with the antibodies for corticosterone (0.06%) and cortisol (1.2%). Assuming a maximum concentration of finasteride in serum of 4 μg/dl (Ohtawa et al, 1991), these cross-reactivities would not significantly affect the assay results.

Table 2. *Method of separation of steroids on celite columns*

Abraham's system 1 (2 g Celite/ml, 1:1 propylene glycol and ethylene glycol)
Progesterone (100%, 3.5 ml)
Dihydrotestosterone (90:10, 3.5 ml)
17-Hydroxyprogesterone (80:20, 3.5 ml)
17-Hydroxypregnenolone (60:40, 5.0 ml)
Abraham's system 2 (2 g Celite/ml, ethylene glycol)
Isooctane wash (1 ml)
Androstenedione (99:1, 3.5 ml)
Dehydroepiandrosterone (95:5, 3.5 ml)
Testosterone (85:15, 3.5 ml)
Estradiol (60:40, 5 ml)
Abraham's system 3 (3 g Celite/ml, 8:2 ethylene glycol and water)
Isooctane wash (2.5 ml)
Deoxycorticosterone (80:20, 3.5 ml)
Corticosterone (70:30, 3.5 ml)
Cortisol (60:40, 5 ml)
Aldosterone (50:50, 5 ml)

Approximately 0.65 g of Celite is tightly packed in a 5-ml glass pipette. Columns are eluted with isooctane : ethyl acetate using step gradients as shown in parentheses.

Statistics

Results are expressed as the mean ± standard error of the mean (SEM). Basal steroid levels, the steroid responses to ACTH, and the product:precursor ratios for the adrenal enzymes before and during finasteride administration were compared by the paired Student's t-test (two-tailed). $P < 0.05$ was considered statistically significant. In order to maximize the sensitivity of detecting statistical differences, no correction was made for multiple comparisons. However, this factor was considered in the interpretation of the results. All statistics were performed with the Microsoft Excel program (Microsoft Corporation, Redmond, Washington) on a Macintosh computer.

Results

During finasteride administration, serum DHT fell from 31 ± 5 to 4.4 ± 1.2 ng/dl ($P < 0.001$). Basal serum concentrations of adrenal steroids before and during finasteride administration are shown in Table 3. Finasteride did not cause a significant change in any of the steroids except DHT. Mean serum concentrations of T and androstenedione increased by 5% and 17%, respectively, a result that would be expected from inhibition of 5α-reductase. However, in neither case did this increase achieve statistical significance.

The response of adrenal steroids to i.v. ACTH is shown in Table 4. Once again, there were no significant differences in any of these responses.

The ratio of products to precursors for intraadrenal enzymes is shown in Table 5. These ratios were determined before and after ACTH stimulation, both before and during finasteride administration. Enzyme inhibition should produce a decrease in the product:precursor ratio, and no such decrease was seen for any enzyme. The ratio androstenedione/17-hydroxyprogesterone increased significantly with finasteride administration (both before and after ACTH administration), most likely as a consequence of inhibition of the 5α-reduction of androstenedione (or T, which can be converted to androstenedione).

Table 3. *Basal steroid levels before (day −7) and during (day 28) finasteride administration*

Steroid	Day −7	Day 28	*P* value
17OH-Pregnenolone (ng/dl)	231 ± 51	198 ± 34	0.49
17OH-Progesterone (ng/dl)	290 ± 30	258 ± 20	0.09
Deoxycorticosterone (ng/dl)	12 ± 1.2	11 ± 1.4	0.39
Corticosterone (μg/dl)	0.37 ± 0.08	0.40 ± 0.09	0.86
Aldosterone (ng/dl)	6.0 ± 0.8	7.8 ± 2.3	0.48
Cortisol (μg/dl)	12 ± 1.6	12 ± 0.9	0.90
Dehydroepiandrosterone (ng/dl)	479 ± 122	366 ± 93	0.33
Androstenedione (ng/dl)	103 ± 16	120 ± 17	0.10
Testosterone (ng/dl)	482 ± 60	507 ± 52	0.29
Dihydrotestosterone (ng/dl)	31 ± 5	4.4 ± 1.2	<0.001

Table 4. *Steroid responses to i.v. ACTH before (day −7) and during (day 28) finasteride administration. The responses for each patient were calculated by subtracting the baseline serum concentration (time 0) from the serum levels present 60 minutes after ACTH administration*

Steroid	Day −7	Day 28	*P* value
17OH-Pregnenolone (ng/dl)	336 ± 108	413 ± 95	0.56
17OH-Progesterone (ng/dl)	95 ± 32	48 ± 27	0.22
Deoxycorticosterone (ng/dl)	16 ± 2	18 ± 3	0.57
Corticosterone (μg/dl)	3.0 ± 0.2	3.4 ± 0.3	0.07
Aldosterone (ng/dl)	6.2 ± 0.9	6.7 ± 1.6	0.79
Cortisol (μg/dl)	14 ± 1	14 ± 2	0.76
Dehydroepiandrosterone (ng/dl)	262 ± 77	298 ± 86	0.78
Androstenedione (ng/dl)	22 ± 10	31 ± 13	0.66

Table 5. *Product : precursor ratios for adrenal enzymes before (day −7) and during (day 28) finasteride administration. SEM is given in parentheses*

Enzyme	Product/precursor	Day −7 0 minutes	Day 28 0 minutes	*P*	Day −7 60 minutes	Day 28 60 minutes	*P*
3b-HSD	17OH-Progesterone/ 17OH-pregnenolone	1.89 (0.42)	1.69 (0.35)	0.68	1.01 (0.35)	0.67 (0.11)	0.68
17,20-Desmolase	Dehydroepiandrosterone/ 17OH-pregnenolone	2.21 (0.26)	1.94 (0.28)	0.48	2.20 (0.95)	1.28 (0.21)	0.38
17,20-Desmolase	Androstenedione/ 17OH-progesterone	0.36 (0.05)	0.47 (0.06)	0.02	0.37 (0.04)	0.46 (0.03)	0.05
17-Ketosteroid reductase	Testosterone/ androstenedione	5.24 (0.69)	4.65 (0.54)	0.23	3.80 (0.38)	3.34 (0.37)	0.17
21-Hydroxylase and 11-hydroxylase	Cortisol/ 17OH-progesterone	0.05 (0.01)	0.05 (0.01)	0.79	0.08 (0.01)	0.09 (0.01)	0.46
11-Hydroxylase	Corticosterone/ deoxycorticosterone	0.03 (0.01)	0.04 (0.01)	0.77	0.13 (0.02)	0.15 (0.02)	0.03
18-Hydroxylase/ dehydrogenase	Aldosterone/ corticosterone	21.3 (3.5)	23.0 (5.2)	0.75	3.85 (0.47)	4.00 (0.47)	0.69

Product : precursor ratios are compared on day −7 and day 28 both before (time 0) and after (time +60) ACTH administration. If finasteride inhibited a particular enzyme, the product : precursor ratio should decrease after ACTH administration because the enzyme activity would be insufficient to handle the increased concentration of precursors.

Conclusions

Finasteride is a synthetic steroid designed to specifically inhibit 5α-reductase. It has previously been shown to have no other hormonal agonist or antagonist activity. Because of its structural similarity to other steroid hormones, we wished to determine if it had any subtle or clinically significant effects on adrenal steroidogenesis. To maximize the chances of seeing such an effect, we measured serum concentrations of relevant steroids before and after ACTH

administration. By increasing the amount of intraadrenal precursors present, ACTH administration should result in a more profound abnormality of product:precursor ratios, if inhibition of adrenal steroidogenesis were present.

We could not detect any inhibition of adrenal steroidogenesis, other than that which would be expected from 5α-reductase inhibition. Serum androstenedione levels did increase by 17% and T by 5%, consistent with a reduction in the metabolism of these steroids by 5α-reductase. Possibly because of biological and assay variability, as well as the small number of subjects, these differences were not statistically significant. In a much larger study in which 297 men received 5 mg finasteride, T levels increased by a mean of 10% within 2 weeks of starting treatment ($P < 0.001$) (Gormley et al, 1992). In the present study, a greater increase was found in serum androstenedione levels compared to serum T levels with finasteride administration. Because androstenedione has no hydroxyl group at the 17-carbon position, it cannot be conjugated to glucuronides or sulfates. Therefore, 5α-reduction is likely to be a quantitatively more important avenue of metabolism for androstenedione than for T.

The most sensitive index of enzyme inhibition is the product to precursor ratio. In no case did finasteride cause a reduction in this ratio, as would be expected with enzyme inhibition. The ratio of androstenedione to 17-hydroxyprogesterone increased with finasteride, both before and after ACTH administration. Again, this is likely due to inhibition of androstenedione metabolism. Although the corticosterone/deoxycorticosterone ratio was slightly increased with finasteride after ACTH stimulation ($P = 0.03$), this change is unlikely to have clinical significance and may be due to chance.

In summary, we find no evidence that finasteride inhibits adrenal steroidogenesis. Its only clinically important hormonal effect is inhibition of 5α-reductase.

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