THE JOURNAL OF INVESTIGATIVE DERMATOLOGY
Vol. 52, No. 1

Printed in U.S.A.

SEBACEOUS GLAND RESPONSE IN MAN TO THE ADMINISTRATION OF TESTOSTERONE, Δ^4-ANDROSTENEDIONE, AND DEHYDROISOANDROSTERONE*

PETER E. POCHI, M.D. AND JOHN S. STRAUSS, M.D.

Previous studies have demonstrated that the sebaceous gland in man is readily stimulated by testosterone (1, 2), and the finding that orchiectomy leads to a reduction in sebaceous gland activity (3) affords evidence that testosterone is primarily responsible for sebaceous gland stimulation in the male. However, the role of other endogenous androgens in the maintenance of sebaceous gland function has not been clearly established. In a prior report we presented some preliminary data on the sebaceous gland response to the administration of dehydroisoandrosterone (4). This study presents results of the effect on sebaceous gland secretion from the administration of Δ^4-androstenedione and dehydroisoandrosterone, androgens which are primarily secreted by the adrenal cortex. Their sebum stimulating potency is compared with that resulting from testosterone administration.

METHOD AND MATERIALS

Various androgens were administered to 27 adult male subjects in 45 separate drug trials and their effect on sebaceous gland secretion studied by an in-vivo assay which has been described previously (2). This consists of the administration of ethinyl estradiol, 1 mg orally daily, until maximum suppression of sebaceous secretion occurs, followed by the concomitant administration of the test androgen. This assay procedure utilizes the observation that estrogen and androgen show no apparent competitive inhibition at the sebaceous gland site (1), and an increase in sebum output during combined estrogen-androgen administration results from the stimulatory effect of the androgen (2).

The following androgens were assayed:

a) methyl testosterone; 5, 10, 25 and 100 mg orally daily, for 8–10 weeks.

b) testosterone, aqueous suspension; 25 mg intramuscularly, 3 times weekly, for 10–11 weeks.

c) testosterone propionate in oil; 25 and 100 mg intramuscularly, 3 times weekly, for 7–11 weeks.

d) Δ^4-androstenedione, aqueous suspension; 25 and 100 mg intramuscularly, for 10–11 weeks.

e) dehydroisoandrosterone, aqueous suspension; 25 and 100 mg intramuscularly, for 8–10 weeks.

In each subject sebum production was measured approximately weekly during each drug trial by a gravimetric procedure (5). The androgenic response was determined by calculating the quantitative difference in sebum production between the average of the last 3 tests in the estrogen suppression period and the average of the last 3 tests during combined estrogen-androgen administration.

RESULTS

Tables I, II, III and IV show the sebaceous gland response to the administration of oral methyl testosterone, intramuscular testosterone preparations, Δ^4-androstenedione, and dehydroisoandrosterone, respectively. An increase in sebum production was observed in each separate drug trial with all the compounds tested. On an equivalent weight basis, methyl testosterone was the most potent androgen tested. Of the dosages used, the greatest rise in sebum secretion was seen with 100 mg of methyl testosterone daily, and the least effect occurred with 25 mg of dehydroisoandrosterone 3 times weekly. However, even in the latter instance, this represented a 40% increase in sebum output.

Statistical analysis of the paired data for each compound and dosage used showed a significant increase ($P < .01$) in sebum production with all doses of methyl testosterone except for the 100 mg daily dose. That the highest dose did not produce a statistically significant response was due largely to the presence of only two subjects in this group. Significant increases were also observed with testosterone ($P < .01$) and with testosterone propionate, 25 mg three times weekly ($P < .05 > .02$). The increases in sebum production resulting from other doses of the androgens used could not be shown to have statistical significance even though, for ex-

Supported in part by research grant AM 07084, National Institutes of Arthritis and Metabolic Diseases, United States Public Health Service.

Presented at the Twenty-ninth Annual Meeting of the Society for Investigative Dermatology, Inc., June 16–18, 1968, San Francisco, Calif.

* From the Department of Dermatology and Evans Memorial Department of Clinical Research, University Hospital, and the Department of Dermatology, Boston University School of Medicine, Boston University Medical Center, Boston, Mass.

TABLE I

Sebaceous gland response to the oral administration of methyl testosterone

Daily dose	Subject	Sebum production (mg lipid/10 cm²/3 hr) Estrogen suppression	Testosterone administration	Increase in sebum (mg)
5 mg	1	0.56	1.60	1.04
	2	0.51	1.67	1.16
	3	0.39	1.27	0.88
	Mean	0.49	1.51	1.02
10 mg	4	1.98	3.60	1.62
	5	1.77	3.40	1.63
	6	1.49	2.97	1.48
	7	1.07	1.98	0.91
	8	0.99	2.76	1.77
	9	0.91	1.66	0.75
	10	0.74	2.39	1.65
	11	0.71	2.56	1.85
	12	0.68	2.45	1.77
	13	0.67	0.88	0.21
	14	0.53	0.85	0.32
	15	0.22	0.99	0.77
	Mean	0.98	2.21	1.23
25 mg	16	1.02	2.45	1.43
	1	0.68	2.07	1.39
	17	0.67	1.46	0.79
	3	0.39	2.04	1.65
	Mean	0.69	2.01	1.32
100 mg	18	0.91	3.66	2.75
	19	0.71	1.39	0.68
	Mean	0.81	2.53	1.72

ample, the 100 mg doses of methyl testosterone, testosterone propionate and Δ^4-androstenedione all resulted in a greater than 200% increase in sebum production. The small number of subjects in most of the groups and the considerable variation from individual to individual in sebum production levels prior to androgenic stimulation prevented statistical validation in these several instances. For these same reasons, dose-response relationships for the individual androgens could not be established by statistical means.

Despite these statistical limitations, it was

TABLE II

Sebaceous gland response to the intramuscular administration of testosterone

Dose	Subject	Sebum production (mg lipid/10 cm²/3 hr) Estrogen suppression	Testosterone administration	Increase in sebum (mg)
Testosterone, 25 mg, 3 times weekly	20	1.41	2.10	0.69
	11	0.84	2.05	1.21
	21	0.76	1.50	0.74
	19	0.68	1.29	0.61
	Mean	0.92	1.74	0.82
Testosterone propionate, 25 mg, 3 times weekly	20	1.21	1.67	0.46
	21	0.82	1.39	0.57
	22	0.76	1.25	0.49
	10	0.62	2.38	1.76
	19	0.51	0.78	0.27
	23	0.47	0.85	0.38
	Mean	0.73	1.39	0.66
Testosterone propionate, 100 mg, 3 times weekly	23	1.13	2.11	0.98
	10	0.71	3.59	2.88
	22	0.39	1.32	0.93
	Mean	0.74	2.34	1.60

TABLE III

Sebaceous gland response to the intramuscular administration of Δ^4-androstenedione

Dose	Subject	Sebum production (mg lipid/10 cm²/3 hr) Estrogen suppression	Δ^4-Androstenedione administration	Increase in sebum (mg)
25 mg, 3 times weekly	24	1.58	2.33	0.75
	25	1.46	1.71	0.25
	10	0.99	1.74	0.75
	Mean	1.34	1.93	0.58
100 mg, 3 times weekly	26	0.81	1.92	1.11
	27	0.31	0.93	0.62
	12	0.29	1.82	1.53
	Mean	0.47	1.56	1.09

still observed that the weaker androgens, Δ^4-androstenedione and dehydroisoandrosterone, were relatively effective in stimulating sebum secretion when compared to testosterone. For example, of the parenterally administered androgens in the dosage of 25 mg three times weekly, it was found that Δ^4-androstenedione was 70% as active as testosterone and 85% as active as testosterone propionate. Dehydroisoandrosterone was 55% and 70% as potent as testosterone and testosterone propionate, respectively.

Eleven subjects received more than one trial of a different androgen, and the effect of these multiple androgen assays in given individuals is shown in Table V. In most instances, these subjects showed appropriate differences in response depending upon the particular androgen and dose used.

TABLE IV

Sebaceous gland response to the intramuscular administration of dehydroisoandrosterone

		Sebum production (mg lipid/10 cm²/3 hr)		
Dose	Subject	Estrogen suppression	Dehydroisoandrosterone administration	Increase in sebum (mg)
25 mg, 3 times weekly	20	1.42	1.83	0.41
	11	1.02	1.77	0.75
	26	1.01	1.24	0.23
	Mean	1.15	1.61	0.46
100 mg, 3 times weekly	20	1.25	2.08	0.83
	22	0.39	1.49	1.10
	Mean	0.82	1.79	0.97

DISCUSSION

It had been observed previously that sebum production in adult males castrated prior to puberty did not differ significantly from that of men castrated after puberty although in both instances sebum levels were higher than those of prepuberal children (6). Since androgen is the only known stimulus for direct sebaceous gland development and secretion (2), it seemed reasonable to infer that adrenocortical androgen was responsible in part for sebaceous gland stimulation. Additional support for this possibility was afforded by the demonstration that the oral administration of prednisone can cause a decrease in sebum output in male castrates and in females, and it has been suggested that this effect is due to suppression of adrenocortical androgens (7).

Thus, the findings in the present study of a significant sebaceous gland stimulating effect from Δ^4-androstenedione and dehydroisoandrosterone, androgens secreted by the adrenal cor-

TABLE V

Comparative sebaceous gland response in individual subjects

	Increase in sebum production (mg)									
Subject	Methyl testosterone (mg/day)				Testosterone (75 mg/week)	Testosterone propionate (mg/week)		Δ^4-Androstenedione (mg/week)		Dehydroisoandrosterone (mg/week)	
	5	10	25	100		75	300	75	300	75	300
1	1.04		1.39								
3	0.88		1.65								
10		1.65				1.76	2.88	0.75			
11		1.85			1.21					0.75	
12		1.77							1.53		
19				0.68	0.61	0.27					
20					0.69	0.46				0.41	0.83
21					0.74	0.57					
22						0.49	0.93				1.10
23						0.38	0.98				
26									1.11	0.23	

tex, offer further evidence of a role for these steroids in sebaceous gland control. The daily secretory rate for Δ^4-androstenedione has been estimated to be 2.7–3.6 mg per day (8, 9) which is less than the doses used in this study. However, the lower dose of dehydroisoandrosterone assayed, i.e. 25 mg 3 times weekly, is in the physiologic range for dehydroisoandrosterone secretion which has been determined to range from 7 to 25 mg daily (10, 11). It may not be possible to relate precisely the physiologic secretion rate for adrenal androgens to the doses administered experimentally. For example, the concentration of dehydroisoandrosterone sulfate in peripheral blood is approximately 100 times that of unconjugated dehydroisoandrosterone (12, 13), with conjugation of dehydroisoandrosterone to sulfate occurring not only in the liver but in the adrenal cortex, itself, prior to its secretion (14). Dehydroisoandrosterone enters this large dehydroisoandrosterone-sulfate pool and, thus, the amount of conjugated steroid reaching peripheral tissues is considerable. It is noteworthy in this regard that Drucker *et al.* reported an increase in sebum production in 2 subjects administered dehydroisoandrosterone sulfate (15). Also, *in vitro* studies have demonstrated the conversion in human skin of dehydroisoandrosterone sulfate to free dehydroisoandrosterone, Δ^4-androstenedione, and testosterone (16).

Since both Δ^4-androstenedione and dehydroisoandrosterone are precursors for testosterone synthesis (17), it is not certain whether sebaceous gland stimulation from adrenal androgens is the result of direct glandular stimulation or of in-vivo conversion to testosterone prior to their reaching the sebaceous gland site. In this connection, several recent reports have shown that human skin can convert dehydroisoandrosterone and/or Δ^4-androstenedione to testosterone *in vitro* (18–20). To what extent these biochemical transformations in the skin occur *in vivo* is not known nor is there any information available from these in-vitro studies as to sites within the skin for such reactivity. However, Baillie and co-workers have demonstrated histochemically the presence of a variety of hydroxysteroid dehydrogenases in human skin, among them 3β- and 17β-dehydrogenases, and the most intense localization for this activity was the sebaceous gland (21). Furthermore, studies on the local application of steroids to the chick comb, another androgen-responsive tissue, show that Δ^4-androstenedione and dehydroisoandrosterone have a significant local stimulating effect (22, 23).

The relative androgenic potency of the steroids administered systemically in this study is in general agreement with that observed in animal assays utilizing the response to stimulation of the seminal vesicles, the ventral prostate gland and the levator ani of rats (24–26) and of the chick comb (27, 28). One exception is that parenterally administered testosterone propionate is 2–7 times as potent as testosterone in animal assays (25, 26); whereas, we found the sebaceous gland to respond somewhat less actively to it than to testosterone.

SUMMARY

An *in vivo* human assay was used to determine the relative stimulating effect of various androgens on sebaceous gland secretion. The androgens studied were methyl testosterone, testosterone, testosterone propionate, Δ^4-androstenedione, and dehydroisoandrosterone. The testosterones were found to be the most potent androgens tested. However, the administration of Δ^4-androstenedione and dehydroisoandrosterone, androgens primarily secreted by the adrenal cortex, also resulted in sebaceous gland stimulation, and this finding suggests a role for these weaker androgens in the control of sebaceous gland function.

REFERENCES

1. Strauss, J. S., Kligman, A. M. and Pochi, P. E.: The effect of androgens and estrogens on human sebaceous glands. J. Invest. Derm., *39:* 139, 1962.
2. Strauss, J. S. and Pochi, P. E.: The human sebaceous gland: its regulation by steroidal hormones and its use as an end organ for assaying androgenicity *in vivo*. Recent. Progr. Hormone Res., *19:* 385, 1963.
3. Pochi, P. E. and Strauss, J. S.: Sebaceous gland function before and after bilateral orchiectomy. Arch. Derm., *88:* 729, 1963.
4. Pochi, P. E., Strauss, J. S. and Mescon, H.: The role of adrenocortical steroids in the control of human sebaceous gland activity. J. Invest. Derm., *41:* 391, 1963.
5. Strauss, J. S. and Pochi, P. E.: The quantitative gravimetric determination of sebum production. J. Invest. Derm., *36:* 293, 1961.
6. Pochi, P. E., Strauss, J. S. and Mescon, H.: Sebum secretion and urinary fractional 17-ketosteroid and total 17-hydroxycorticoid excretion in male castrates. J. Invest. Derm., *39:* 475, 1962.

7. Pochi, P. E. and Strauss, J. S.: Effect of prednisone on sebaceous gland secretion. J. Invest. Derm., *49:* 456, 1967.
8. Horton, R. and Tait, J. F.: Androstenedione production and interconversion rates measured in peripheral blood and studies on the possible site of its conversion to testosterone. J. Clin. Invest., *45:* 301, 1966.
9. Rivarola, M. A., Saez, J. M., Meyer, W. J., Jenkins, M. E. and Migeon, C. J.: Metabolic clearance rate and blood production rate of testosterone and androst-4-ene-3,17-dione under basal conditions, ACTH and HCG stimulation. Comparison with urinary production rate of testosterone. J. Clin. Endocr., *26:* 1208, 1966.
10. Vande Wiele, R. L., MacDonald, P. C., Bolte, E. and Lieberman, S.: Precursors of the urinary 11-desoxy-17-ketosteroids: estimation of the secretory rate of dehydroisoandrosterone. J. Clin. Endocr., *22:* 1207, 1962.
11. Horton, R. and Tait, J. F.: *In vivo* conversion of dehydroisoandrosterone to plasma androstenedione and testosterone in man. J. Clin. Endocr., *27:* 79, 1967.
12. Vihko, R.: Gas chromatographic-mass spectrometric studies on solvolyzable steroids in human peripheral plasma. Acta Endocr., *52:* (suppl. 109), 1966.
13. Saroff, J., Keenan, R. E., Sandberg, A. A. and Slaunwhite, W. R., Jr.: Determination of testosterone, androstenedione, and dehydroepiandrosterone in human plasma using bromine-82. Steroids, *10:* 15, 1967.
14. Baulieu, E., Corpéchot, C., Dray, F., Emiliozzi, R., Lebeau, M., Mauvais-Jarvis, P. and Robel, P.: An adrenal-secreted "androgen": dehydroisoandrosterone sulfate. Its metabolism and a tentative generalization on the metabolism of other steroid conjugates in man. Recent. Progr. Hormone Res., *21:* 411, 1965.
15. Drucker, W. D., Blumberg, J. M. and David, R.: Dehydroepiandrosterone-sulfate: biologic activity in man. Clin. Res., *14:* 279, 1966.
16. Kim, M. H. and Herrmann, W. L.: *In vitro* metabolism of dehydroepiandrosterone sulfate in foreskin, abdominal skin and vaginal mucosa. J. Clin. Endocr., *28:* 187, 1968.
17. Lucis, O. J., Raheja, M. C., Millard, O. and Morse, W. I.: Utilization of circulating precursors for the synthesis of testosterone by human testis in vivo. Canad. J. Biochem., *45:* 1213, 1967.
18. Cameron, E. H. D., Baillie, A. H., Grant, J. K., Milne, J. A. and Thomson, J.: Transformation *in vitro* of (7α-^{3}H) dehydroepiandrosterone to (^{3}H) testosterone by skin from men. J. Endocr., *35:* XIX, 1966.
19. Gallegos, A. J. and Berliner, D. L.: Transformation and conjugation of dehydroepiandrosterone by human skin. J. Clin. Endocr., *27:* 1214, 1967.
20. Gomez, E. C. and Hsia, S. L.: *In vitro* metabolism of testosterone-4-^{14}C and Δ^{4}-androstene-3,17-dione-4-^{14}C in human skin. Biochemistry (Wash.), *7:* 24, 1968.
21. Baillie, A. H., Ferguson, M. M. and Hart, D. McK.: *Developments in Steroid Histochemistry*, Academic Press, London, 1966.
22. Ofner, P., Harvey, H. H., Sasse, J., Munson, P. L. and Ryan, K. J.: A comparison of some biological characteristics of Δ^{1}- and Δ^{4}-3-ketosteroids of the androstane series. Endocrinology, *70:* 149, 1962.
23. Dorfman, R. I. and Dorfman, A. S.: Assays of androgens administered by inunction to the chick's comb. Acta Endocr., *42:* (suppl. 74), 1963.
24. Segaloff, A. and Gabbard, R. B.: Steroid structure and androgenicity. Endocrinology, *71:* 949, 1962.
25. Dorfman, R. I. and Dorfman, A. S.: The assay of subcutaneously injected androgens in the castrated rat. Acta Endocr., *42:* 245, 1963.
26. Edgren, R. A.: A comparative study of the anabolic and androgenic effects of various steroids. Acta Endocr., *44:* (suppl. 87), 1963.
27. Dorfman, R. I. and Dorfman, A. S.: Assay of subcutaneously administered androgens on the chick's comb. Acta Endocr., *41:* 101, 1962.
28. Dorfman, R. I. and Dorfman, A. S.: The assay of orally administered androgens using the chick's comb. Acta Endocr., *42:* 240, 1963.