Comparison of the Effects of Six Antiandrogens on Chick Comb Stimulation by Testosterone (34926)

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Several compounds with significant antiandrogenic activity in laboratory animals have been described (1–5). These reports have dealt with the antiandrogenic properties of a single compound or with comparisons of closely related analogs. The relative activities of the major antiandrogens, determined concurrently by the same procedure, have apparently not been reported. This paper presents data on six antiandrogens tested simultaneously for their ability to antagonize the stimulant effect of testosterone on chick comb weight. The structures of the compounds studied are shown in Fig. 1.

Methods. One-day-old White Leghorn cockerels obtained from the Kerr Hatchery, Frenchtown, New Jersey were injected sc once daily for 7 consecutive days with testosterone (T) at a dosage of 288 μg/day in 0.1 ml/day of sesame oil. Antagonists were administered sc by separate injection at a different body site in 0.2 ml/day of sesame oil at dosages of 1, 3, 9, and 27 times T on a molar basis. Control chicks were injected sc with sesame oil. All chicks were autopsied on the day after the last treatment day and comb ratios (mg comb/g of body wt) were determined.

Results. All of the antiandrogens, except A-norprogesterone, were effective antagonists of the chick comb response to T (Table I). Complete suppression of comb weight stimulation by T was observed with cyproterone acetate and Ro 5-2537. Maximal observed inhibitions for the other active compounds were 79% for Ro 2-7239, 83% for methyl, B-nortestosterone and 57% for cyproterone (free OH). Unesterified cyproterone and Ro 2-7239 showed poor linearity of log dose–response within the experimental dose range. Cyproterone acetate gave a linear log

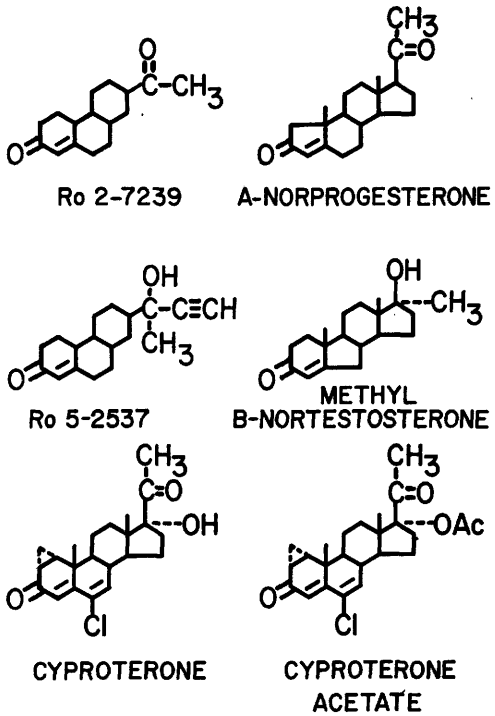

FIG. 1. Structures of compounds studied.

dose–response with the methyl, B-nortestosterone curve almost parallel at the high dosage end of the curve. At 27 × T cyproterone acetate-treated chicks had a mean comb ratio which was significantly less than that of vehicle-treated controls. The log dose–response curve for Ro 5-2537 was linear and had a steeper slope than the cyproterone acetate and methyl, B-nortestosterone curves.

Discussion. The difficulties inherent in determining the relative potencies of two or more compounds, each with similar qualitative activity on a biological parameter but which differ in quantitative effects, are demonstrated in this study. Presumably, the

TABLE I. Effects of Various Antiandrogens on Chick Comb Weight Response to Testosterone.[a]

Treatment	Molar ratio × T	N	Mean ± SE comb ratio	t tests[b] vs T	t tests[b] vs C
Control (C)	—	38	0.42 ± 0.02	***	—
Testosterone (T)	—	38	0.89 ± 0.04	—	***
Ro 2-7239	1	17	0.73 ± 0.04	*	***
	3	13	0.81 ± 0.06	NS	***
	9	15	0.53 ± 0.04	***	**
	27	15	0.52 ± 0.04	***	*
A-Norprogesterone	1	17	0.94 ± 0.05	NS	***
	3	10	0.72 ± 0.09	NS	***
	9	15	0.83 ± 0.06	NS	***
	27	15	0.75 ± 0.06	NS	***
Ro 5-2537	1	17	0.80 ± 0.04	NS	***
	3	14	0.73 ± 0.07	*	***
	9	14	0.57 ± 0.04	***	***
	27	14	0.41 ± 0.03	***	NS
Methyl, B-nortestosterone	1	14	0.63 ± 0.05	***	***
	3	12	0.64 ± 0.09	**	***
	9	13	0.55 ± 0.06	***	**
	27	15	0.50 ± 0.02	***	*
Cyproterone	1	14	0.74 ± 0.05	*	***
	3	15	0.82 ± 0.07	NS	***
	9	12	0.62 ± 0.04	**	***
	27	16	0.68 ± 0.05	**	***
Cyproterone acetate	1	14	0.53 ± 0.04	***	**
	3	12	0.46 ± 0.02	***	NS
	9	12	0.39 ± 0.02	***	NS
	27	14	0.30 ± 0.01	***	***

[a] All chicks except Controls received 288 μg of testosterone sc/day.
[b] * $p < .05$; ** $p < .01$; *** $p < .001$; NS = not significant.

antiandrogens examined are all competitive antagonists of testosterone at target organ receptor sites. However, alterations in chemical structures result in different patterns and rates of absorption, distribution, metabolism, and excretion, as well as different affinities for androgen receptors. With the compounds examined in the present study, additional complications arise, since some of the compounds suppress pituitary gonadotropin secretion thus reducing the endogenous supply of androgen. Cyproterone acetate at 27 × T reduced the mean comb ratio significantly below the control level. This could be due to antagonism of endogenous androgen peripherally and/or antigonadotropic activity. Ro 2-7239 has inherent androgenicity which could contribute to the comb weight. Consequently, it is not surprising that exact estimates of relative potencies were precluded by poor linearity of log dose–response curves with some compounds, and lack of parallelism of curves for others.

Of the six compounds tested cyproterone acetate showed the highest antiandrogenic potency. At a 1:1 ratio against T, significant antagonism was observed and complete suppression occurred at a ratio of 3:1. Ro 5-2537 was significantly antiandrogenic at a ratio of 3:1 with complete suppression of T at 27:1. Ro 2-7239, methyl, B-nortestosterone and unesterified cyproterone did not manifest complete antagonism of T within the dosage range studied.

Summary. Six antiandrogens were compared for ability to inhibit the stimulant effect of testosterone on chick comb weight. Relative potencies could not be determined exactly because of nonparallelism of the dose–response curves. Based upon the maximal inhibitions observed, relative potencies were as follows: cyproterone acetate > Ro 5-2537 > methyl, B-nortestosterone > Ro 2-7239 > cyproterone (free OH). A-Norprogesterone was inactive as an antiandrogen at dosages up to 27 × T on a molar basis.

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