HORMONAL CHANGES AND HAIR GROWTH DURING TREATMENT OF HIRSUTISM WITH CIMETIDINE

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SUMMARY

The effects on hair growth by treatment with cimetidine have been studied. This drug has been given orally to 4 women with simple hirsutism and 3 women with peptic ulcer as controls for a period of 9 months.

Hair growth slowed down in all of the treated women but the results were not statistically significant.

A significant decrease in urine 17-ketosteroids has been observed, while plasma levels of testosterone, 17-βestradiol, progesterone, FSH, LH and prolactin, did not change substantially.

It is concluded that, on the whole, cimetidine doses not seem to induce such results on hair growth as to claim a rôle in the treatment of hirsutism in other current regimes.

INTRODUCTION

Long considered a merely aestetical problem, hirsutism has only recently drawn attention for its medical aspects. Even more recently encouraging therapeutical results have been obtained with drugs derived from hormones having anti-androgenic properties. Similar properties have been displayed by substances, like cimetidine, acting upon the synaptic receptors, in the experimental animal. The mode of action of this drugs seems to involve, besides an increase of the incretion of prolactin, an inhibition of the transferral of dihydrotestosterone to androgen-receptor sites (Vigersky *et al.*). In fact these Authors were able to achieve interesting results treating 5 hirsute women with cimetidine. This preliminary report was not however, followed by any other published experience by the same or other researchers. Given the importance of the topic we sought to verify the effect of treatment with cimetidine in a series of hirsute women.

MATERIAL AND METHODS

We studied 7 women aged 19-24 years who had hirsutism with no other associated disorders and regular menses. Oral cimetidine was given in a dosage of 600 mg twice daily for two months, thereafter 400 mg once daily for seven months. We also studied a control group of 3 women of comparable age who were taking cimetidine for peptic ulcer but where otherwise healthy.

Each subject in the study underwent the following investigations: urine 17-ketosteroids (according to Albright *et al.*, modified); plasma testosterone, 17-β-estradiol, progesterone, FSH, LH, prolactin. Plasma assays were all carried out by means of radioimmunoassay methods. Urine and plasma specimens were taken between the 10th and 14th day of the period, before treatment and after 2 and 9 months. The effects of treatment on hair growth have been evaluated by weighing the hair shaved off a given area in the lateral surface of the thigh before and at the end of the study.

All subjects gave their informed consent to participate in the study. None was pregnant during the study period. Results are expressed

Table 1. — *17-Ketosteroids.*

No.	A Basal	B 3 months	C 9 months
1	24.6	22.3	19.6
2	21.3	18.8	19.1
3	21.8	16.3	17.1
4	19.6	15.3	16.1
5	20.3	21.3	19.8
6	22.0	—	20.6
7	19.8	17.1	—
	21.3	18.5	18.7
DS ±	1.7	2.8	1.7
Student t	A−B=P<0.5 100%	AC=P<0.5 87%	B−C=NS 88%

Table 2. — *Testosterone.*

No.	A Basal	B 3 months	C 9 months
1	1.10	1.16	0.96
2	0.98	0.90	0.88
3	1.16	1.20	1.02
4	1.02	0.96	1.08
5	2.61	1.48	1.63
6	1.11	1.04	0.92
7	2.00	—	1.52
	1.43	1.12	1.14
DS ±	0.6	0.2	0.3
Student t	A−B=NS 100%	A−C=NS 78%	B−C=NS 80%

as means and SD. Student's paired and two-sample T-test was used in the statisticaly analysis.

RESULTS

Urine 17-KS decreased significantly ($P<0.05$) after cimetidine treatment, from the initial level (21.3 ± 17 mg/24 h) to 18.5 ± 2.8 at two months and 18.7 ± 1.7 at nine months. Small, non significant, decreases have also been observed in plasma testosterone levels from the baseline value of 1.43 ± 0.6 ng/ml to 1.12 ± 0.2 and 1.14 ± 0.3 at two and nine months, respectively.

An inconsistent trend was displayed by 17 β-estradiol which after increasing from 344.8 pg/ml to 356 ± 49.4 after two months, went down to levels lower than the initial ones after nine months of treatment (328.2 ± 55.5). Neither were these variations statistically significant, nor those of progesterone (1.5 ± 0.5 ng/ml and 1.3 ± 0.3, 1.4 ± 0.3, respectively). Similarly, no significant changes were observed in the levels of FSH, LH and prolactin (table 1).

As to hair growth, it seems to slow down in treated subjects after treatment with cimetidine. In fact hair weight falls from 28.0 ± 6.1 mg to 24.5 ± 4.6. This

Table 3. — *17-β-estradiol.*

No.	A Basal	B 3 months	C 9 months
1	371	350	348
2	397	401	386
3	412	388	363
4	216	275	241
5	286	—	280
6	387	366	351
	344.8	356.0	328.2
DS ±	77.1	49.4	55.5
Student t	A+B=NS 100%	B−C=P<0.5 103%	A−C=NS 95.1%

Table 4. — *Progesterone.*

No.	A Basal	B 3 months	C 9 months
1	1.6	1.4	1.4
2	0.75	1.0	0.95
3	0.85	0.95	1.05
4	2.0	1.60	1.55
5	1.65	1.40	1.35
6	1.86	1.44	1.52
7	1.90	—	1.83
	1.5	1.3	1.4
DS ±	0.5	0.3	0.3
Student t	A−B=NS 100%	A−C=NS 86.6%	A−C=NS 93%

Table 5. — *FSH.*

No.	A Basal	B 3 months	C 9 months
1	18	19	22
2	23	21	24
3	16	23	21
4	28	26	20
5	23	24	21
6	31	29	—
7	26	23	24
	23.6	23.6	22.0
DS ±	5.3	3.3	1.7
Student t	A−B=NS 100%	A−C=NS 100%	B−C=NS 93%

Table 6. — *LH.*

No.	A Basal	B 3 months	C 9 months
1	44	—	29
2	56	50	52
3	66	63	58
4	41	49	55
5	57	62	59
6	49	40	42
7	—	55	43
	52.2	53.2	48.3
DS ±	9.3	8.7	10.9
Student t	A−B=NS 100%	B−C=NS 102%	A−C=NS 92.5%

change however, is not significant and does not differ from that observed in control subjectes (table 1).

Treatment with cimetidine did not bring about any side-effects. In particular, no troubles with menstrual function or changes in libido or galactorrhea were observed.

DISCUSSION

The variety of therapeutical approaches to hirsutism implies by itself that so far there is no effective and safe treatment available. As a consequence there is a justification in trying out new drugs although, as in the case of cimetidine, there appears to be no theoretical background for its use, but only a casual finding of a possible beneficial effect.

Table 7. — *HPRL.*

No.	Basal A	9 months B
1	18	19
2	11	14
3	21	25
4	20	21
5	12	15
6	7	6
7	19	18
	15.4	16.9
DS ±	5.4	6.0
Student t	A−B=NS 100%	109.7%

Table 8. — *Hair weight.*

No. (hirsutism)	A Basal	B 9 months
1	21.6	19.9
2	32.8	30.1
3	24.1	21.8
4	33.7	26.3
	28.0	24.5
DS ±	6.1	4.6
Student t	A−B=NS 100%	87.5%

Table 9. — *Hair weight.*

No. (normal)	A Basal	B 9 months
1	8.4	7.9
2	11.3	10.6
3	17.1	13.2
	12.3	10.6
DS ±	4.4	2.6
Student t	A−B=NS 100%	86.2%

Table 10.

	A Baseline values	B 2 months	C 9 months	Student t
17-KS (7-20 mg/24 h)	21.3	18.5	18.7	A−B=p<0.5
	±1.7	±2.8	±1.7	A−C=p<0.5
	100%	87%	88%	B−C=NS
Testosterone (0.1-0.9 ng/ml)	1.43	1.12	1.14	A−B=NS
	±0.6	±0.2	±0.3	A−C=NS
	100%	78%	80%	
17-βE_2 (200-400 pg/ml, mid-cycle)	344.8	356.0	328.2	A−B=NS
	±77.1	±49.4	55.5	B−C=p<0.05
	100%	103%	95%	A−C=NS
Progesterone (0.15-1.8 ng/ml, mid-cycle)	1.5	1.3	1.4	A−B=NS
	±0.5	±0.3	±0.3	A−C=NS
	100%	87%	93%	B−C=NS
FSH (15-30 mUI/ml, mid-cycle)	23.6	23.6	22.0	A−B=NS
	±5.3	±3.3	±1.7	A−C=NS
	100%	100%	93%	B−C=NS
LH (30-60 mUI/ml, mid-cycle)	52.2	53.2	48.3	A−B=NS
	±9.3	±8.7	±10.9	A−C=NS
	100%	102%	92%	B−C=NS
HPRL (5-25 ng/ml)	15.4		16.9	
	±5.4		±6.0	A−C=NS
	100%		110%	
Hair weight (mg) hirsute W.	28.0		24.5	
	±6.1		±4.6	A−C=NS
	100%		87%	
Control	12.3		10.6	
	±4.4		±2.6	A−C=NS
	100%		86%	

Our data confirm that a decrease in hair growth can be induced by cimetidine, both in hirsute and "control" women, although to a much lesser degree than that reported by Vigersky *et al.* It has to be stressed, on the one hand, that a diminished hair growth, if modest, has been consistently observed in all subjects of our series; on the other hand, the lack of statistical significance may well be due to the small number of observations.

The mechanisms whereby cimetidine can affect hair growth are unclear. Some clue, however, can be provided by the behaviour of the hormones we have studied. A significant downward trend in urinary 17-KS showed up throughout the study. A similar, though not significant, change in testosterone was found. It is therefore possible that this might explain the effects on hair growth of cimetidine acting, by means of a different peripheral metabolization of adrenal precursors of urinary androgens (in the absence of any known effect of cimetidine direct on the adrenal gland or on ACTH release). In

fact, in most cases of simple hirsutism higher levels of adrenal androgens can be detected (Grandesso and Spandri). Conversely, all of the means that induce a lowering of the levels of urine 17-KS are also able to bring about, at the same time, a stabilization or, more often, a slowing down of hair growth.

This interpretation is not in contrast with that of Vigersky *et al.*, who, not finding in their study any significant decrease in urine 17-KS or plasma testosterone and dihydrotestosterone, put forward the hypothesis that cimetidine may act through an inhibition of the effects of testosterone at the receptor site, as already proposed by Funder and Mercier and by Winters *et al.* The small but significant changes observed in 17 β-estradiol are more difficult to interpret, since there seems to be no known effect of cimetidine on ovarian steroidogenesis. In our study progesterone, FSH, LH and prolactine levels were unaffected by treatment, so confirming the results obtained by Nelis in 13 males with peptic ulcer and 15 healthy controls. In a smaller series of three male patients however, Peden has observed after a longstanding treatment with cimetidine an increase in FSH in two and of LH in one of them. LH levels did not change after treatment in the series reported by Vigersky *et al.*

Contrasting results have also been found as regards the effects of cimetidine on the levels of prolactin. While a number of Authors did not detect any significant change (Nelis, Cavallini *et al.*, Rowley-Jones, Valcavi *et al.*), Peden *et al.* and Delle Fave *et al.* reported higher levels of prolactin after treatment.

According to Sharpe *et al.*, the different effects of cimetidine treatment may be explained by the different route of administration. Central pathways controlling TRH and PIF release may only be affected by cimetidine when it gets through the hemato-encephalic barrier. This only occurs at the higher plasma levels that can be reached by intravenous, hardly by oral administration.

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