TESTOSTERONE, 17 KS, 17βE$_2$ FSH-LH VARIATIONS AND HIRSUTISM MODIFICATIONS DURING SPIRONOLACTONE THERAPY

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SUMMARY

The research here reported concerns 9 hirsute women, four of them with PCO and five with idiopathic hirsutism, who underwent treatment with spironolactone.

4 non hirsute hypertensive cases served as control. For one year hair growth, testosterone, 17 Ks, estradiol and gonadotropins behaviours were studied in all of the patients.

Results clearly show that the peripherical response (the hair) to the therapy is only just sufficient, and corresponds to a good reduction of the androgenic hormones in blood. However, there is also an LH gonadotropin secretion reduction which is statistically scarcely significant.

If the therapeutic response of hair were good, fetal risk could be prevented with safe and contemporaneous contraception. However, since the response is scarcely sufficient, we do not think this therapy is more advisable than other ones.

Corticosteroids, contraceptives, ciproterone, cymetidine and spironolactone (S) can be used in hirsutism therapy. Such substances were used both in the so called idiopathic hirsutism and in polycystic ovary (PCO), but none of them gained an advantage over the others since the results we got are neither regular nor surely positive. The presence of several side-effects, sometimes badly tolerated, should be mentioned, as they can compromise the therapy: corticosteroids can lead to hypertension and diabetes, ciproterone to amenorrhea and fetal damage, cymetidine to fetal damage, and contraceptives to hypertension, venous thrombosis, diabetes and hepatic damage.

As far as S is concerned, nothing has yet been said in literature against its use, except for one article that points out ureteral and prostatic damages in male fetuses of pregnant rats treated with 40 mg of S per day, which is definitely a very high dose ([1]). After the first clinical report ([2]) on the scarce or null changes aroused by S in the hormonal balance of patients that underwent hypotensive therapy, other reports followed ([3, 4]) that confirmed the scarce androgen changes in hypertensive male patients. Then, an important testosterone (T) fall was signalized ([5]) in a case of PCO treated with 200 mg of S per day for hypertension. In that case, considerable estradiol (E_2) decrease occurred too. Other Authors ([6]) corroborated the androgen fall in hirsute patients treated with 50 mg of S per day, and also indicated its probable action mechanism. 30 hirsute women were treated with 200 mg of S per day from the 4th to the 21st day of their cycle ([7]): testosterone (T) fall was confirmed and an E_2 increase was seen in 25 of the 30 cases.

In 39 cases of hirsute patients a better therapeutic effect was achieved in idiopathic forms than in those caused by PCO ([8]), with no mention of estrogens and without any important T variation. In none of the reports we quoted was

any other side-effect signalled that could check its use and testing, that in some cases lasted even more than 12 months. Apart from the E_2 secretion (of which we still do not know whether it is curbed, increased, or whether it stays unchanged during S therapy), there are different opinions also on gonadotropin LH and FSH secretion variations. Some Authors [7] believe that gonadotropin decreases, some others [4] that LH gonadotropin first increases and then gets back to normal, others again believe that both gonadotropins stay unchanged [9, 16]. We then consider it useful to report the results we got in the treatment of hirsutism with S, and to signal E_2 and gonadotropin variations.

MATERIAL AND METHODS

We treated 9 women, aged 18 to 30 (average 24), suffering from hirsutism of medium gravity with 100 mg of S (50 mg every 12 hours). We excluded all the forms imputable to drugs or to a major endocrine pathology. There were 4 cases with PCO (cases number 1, 5, 6 and 7), and 5 with the so called idiopathic hirsutism. 2 cases presented oligomenorrhea (both with PCO), and 1 case had amenorrhea for 3 months. The drug was administered from the 4th to the 21st day of every month following the cycle or assuming it in case of amenorrhea, which was quite easy since the last menses dated back to 3 months earlier. Such treatment was maintained for 12 months, and during that period neither barbituric and antalgic drugs nor hormonal products were assumed by the patients. Blood samples for hormonal assessments were withdrawn 1, 4, and 12 months after the treatment was started. After 1, 4, 9 and 12 months hair growth was checked by shaving each time the same area of the thigh [10]. As control subjects we chose 4 hypertensive women, age range 26 to 32 (average 29), who were starting antihypertensive treatment with 50 or 100 mg of S every 12 hours. 3 cases went on with this therapy, while in one case hypertension control also required hydrazinophtalazine. No statistical research was made on these patients (only 4).

In order to get uniform data, blood withdrawals and hair shaving were done during the week when the ovular peak happened; in the presumably anovulatory patients blood samples were withdrawn during the theoretic ovulation period, that is roughly by the middle of the cycle.

Table 1. — *Basal and during Spironolactone therapy testosterone values in 9 hirsute women.*

Case No.	Testosterone (v.n. 0.1-0.9 ng/ml) Basal	After 1 month	After 4 months	After 12 months
1	1.21	1.16	0.61	0.58
2	2.06	1.86	0.68	—
3	2.13	2.10	1.00	0.91
4	2.35	2.16	0.93	0.60
5	1.68	2.00	1.24	1.16
6	0.83	0.46	0.44	1.10
7	2.37	1.81	0.83	0.98
8	1.62	1.48	1.57	0.88
9	1.84	2.10	1.13	0.73
Mean	1.79	1.68	0.94	0.87
± SD	±0.52	±0.56	±0.35	±0.22
Group	A	B	C	D
t Student: A−B=n.s.; A−C=p<0.01; A−D=p<0.01				
	100%	93%	52%	48%

RESULTS

FSH, LH and E_2 basal values were superposable and normal in both groups (tabs. 3, 4, 5, 6). The T and the 17 KS were distinctly higher than normal in hirsute women, while they were normal in hypertensive patients (tabs. 1, 2, 6). After one month of therapy *hirsute* women showed no statistically significant variations of T (−7%), of 17 KS (no variations), of E_2 (−2%) and of gonadotropin FSH (−4%) and LH (−10%) (see tables 1, 2, 3, 4, 5). Hypertensive and *non hirsute* patients showed the following variations: T +3%, 17 KS −13%, E_2 −5%, FSH +16%, LH −11% (see tab. 6).

After four months of therapy *hirsute* women showed the following variations: T −48% ($p<0.01$), 17 KS −56% ($p<0.001$), E_2 +2% (n. s.), FSH gonadotropin −16% ($p<0.05$) and LH gonadotropin −20% ($p<0.01$). After 12 months *hirsute* women showed the same values of T and 17 KS they had at the

Table 2. — *Basal and during Spironolactone therapy urinary 17 KS values in 9 hirsute women*

Case No.	17 KS (v.n. 7-20 mg/24 h) Basal	After 1 month	After 4 months	After 12 months
1	26.2	25.8	11.3	8.1
2	23.3	24.6	8.1	7.9
3	25.1	28.1	6.9	8.1
4	17.3	20.1	8.8	8.4
5	21.8	16.3	16.3	12.0
6	18.6	15.8	9.2	10.6
7	20.6	19.6	11.1	10.3
8	25.9	26.6	8.9	—
9	19.3	21.3	6.6	—
Mean	22.01	22.02	9.69	9.34
± SD	±3.30	±4.46	±2.95	±1.51
Group	A	B	C	D
t Student: A−B=n.s.; A−C=p<0.001; A−D=p<0.001				
	100%	100%	44%	42%

fourth month (respectively −52% and −58%); E_2 (+3%) and FSH gonadotropin (−15%) did not change since the fourth month of therapy, while LH gonadotropin dropped from 20% to 26%. Statistical inquiry concerning basal values showed: T=p<0.01; 17 KS=p<0.001; E_2=n. s.; FSH=p<0.05; LH=p<0.05.

Hypertense *non hirsute* control patients showed the following non significant variations: T −12%, KS −18%, E_2 −4%, FSH gonadotropin +4% and LH gonadotropin −7%.

With regard to hair growth, *hirsute* women showed no variation after one month, but after four months there was regression of 20%, after 9 months of 17% and after one year of 22%. The hair was less thick, thinner, and its color was lighter (see tab. 7). Since the *non hirsute* patients had almost no hair problems, we thought that a control would be useless. We saw no oligomenorrhea variations in the two cases suffering from it (PCO), while in case number 3 (idiopathic hirsutism) amenorrhea disappeared during the third month of therapy. Seven patients out of nine had polyuria that lasted 4 to 10 days at the beginning of the treatment; one case presented frontal headache during the first days of therapy; four of the seven polyuric patients initially showed weariness and astenia, but there was no need to suspend or modify the treatment in any of the cases. The 4 control cases only showed a slight polyuria during the first days of therapy. Menstrual cycles staid unchanged or underwent very little rhythm variations.

COMMENT

The peripherical effect of S on hair, unlike what some Authors said ([8]), did not occur after a few weeks but after 3 or 4 months, and kept to the same values for the rest of the treatment (12 months). Not only was the response quantitative, but also a reduction in thickness and length was noticed.

It is interesting to remark that T and 17 KS reduction went together with hair

Table 3. — *Basal and during Spironolactone therapy 17-β estradiol values in 9 hirsute women.*

Case No.	Estradiol (v.n. 200-400 pg*ml, mid-cycle) Basal	After 1 month	After 4 months	After 12 months
1	263	284	280	310
2	195	216	176	215
3	342	358	358	376
4	306	327	351	340
5	215	296	270	251
6	353	228	415	389
7	417	336	376	351
8	380	315	295	316
9	361	419	389	386
Mean	314	308	323	325
± SD	±7.59	±6.28	±7.47	±6.03
Group	A	B	C	D
t Student: A−B=n.s.; A−C=n.s.; A−D=n.s.				
	100%	98%	102%	103%

Table 4. — *Basal and during Spironolactone therapy FSH values in 9 hirsute women.*

Case No.	FSH (v.n. 15-30 mUI/ml, mid-cycle) Basal	After 1 month	After 4 months	After 12 months
1	32.8	28.6	20.3	22.5
2	33.6	35.0	26.2	25.6
3	21.5	20.5	20.3	23.1
4	18.6	20.3	18.1	16.7
5	35.9	30.6	27.3	25.9
6	33.1	32.8	21.3	28.6
7	27.0	25.9	26.9	24.9
8	28.1	24.7	25.5	—
9	28.7	31.3	27.1	—
Mean	28.8	27.7	23.67	23.9
±SD	±5.81	±5.25	±3.61	±3.75
Group	A	B	C	D
t Student: A−B=n.s.; A−C=p<0.05; A−D=p<0.05				
	100%	96%	84%	85%

reduction; those two hormonal dosages seemed therefore to be enough, in most of the cases, to assess S therapeutic effect: the two hormones decrement corresponds to a slight hair reduction. We agree with the Authors [7] who say it is impossible to foresee therapeutic effect considering T and 17 KS initial values. We wish to add that peripherical response (hair reduction) can be considered as being satisfactory or at least visible, when there is a reduction of T and 17 KS, regardless of their initial values. Such effect starts at the third or fourth month of therapy and then becomes stable. It is interesting to notice that the only two T values still over the normal limit after 12 months of treatment were those of two PCO cases. The same two cases and a third one also with PCO had, compared to the 9 patients group, the highest values (but still within the normal limit) of 17 KS too. Androgenic hormonal response is therefore slower in PCO than in idiopathic hirsutism; in fact hair reduction is 24.4% in idiopathic hirsutism and 17% in PCO.

We understand from literature that S action is multiple [5, 11, 12, 14, 15]:

– it is competitive on dihydrotestosterone receptors, and does not increase T convertion into E_2 (our data confirm this second point);

– it reduces T synthesis;

– it increases T metabolic clearance and reduces its hydroxylation;

Table 5. — *Basal and during Spironolactone therapy LH values in 9 hirsute women.*

Case No.	(LH (v.n. 30-60 mUI/ml, mid-cycle) Basal	After 1 month	After 4 months	After 12 months
1	48.1	46.3	40.7	36.8
2	37.3	39.1	31.6	29.5
3	26.2	28.3	23.2	21.7
4	31.4	36.3	29.3	28.1
5	40.3	38.2	31.8	33.8
6	51.5	45.7	40.6	36.9
7	57.6	49.6	33.7	35.8
8	63.1	50.1	51.9	—
9	29.2	18.3	21.8	30.1
Mean	42.74	39.13	33.84	31.81
±SD	±13.05	±10.51	±9.40	±5.56
Group	A	B	C	D
t Student: A−B=n.s.; A−C=p<0.01; A−D=p<0.05				
	100%	90%	80%	73.9%

Table 6. — *Testosterone (T), urinary 17 KS, 17-β estradiol (E_2), FSH and LH basal and during Spironolactone therapy values (Mean±SD) in 4 non hirsute hypertensive women.*

	T	17 KS	E_2	FSH	LH
Basal	0.61 ±0.08	12.3 ±4.8	4.16 ±5.9	24.1 ±3.6	54.10 ±6.3
After 1 month	0.63 ±0.11	10.8 ±2.3	3.96 ±8.8 (3 cases)	28.0 ±7.9	48.1 ±3.3
After 12 months	0.54 ±0.09	10.6 ±4.2 (3 cases)	4.01 ±6.3	25.7 ±4.2	50.6 ±8.9

Table 7. — *Hair measurement (in mg) before and during Spironolactone therapy in 9 hirsute women.*

Case No.	Hair (mg) Basal	1 month	After 4 months	After 9 months	After 12 months
1	43.6	41.3	38.6	40.0	33.1
2	29.1	27.3	15.8	13.1	12.8
3	31.6	32.1	35.7	31.7	—
4	19.4	16.2	21.4	24.6	13.9
5	21.7	11.8	13.6	12.9	15.6
6	23.5	—	18.0	23.8	—
7	40.2	39.6	26.6	—	28.2
8	37.6	34.1	27.1	30.8	39.0
9	35.0	36.3	29.9	—	28.6
Mean	31.3	29.8	25.1	25.3	24.45
	8.5	10.7	8.7	9.9	10.3
±DS	100%	95%	80.5%	80.8%	78.2%

– it inhibits its fixation to cutaneous receptors.

All these attack points conform to ovarian and adrenal hormones' androgenic category, and particularly to T, its precursors and its derivatives.

However, we cannot ignore that both gonadotropins also decrease and therefore, if the main effect is the antiandrogenic peripherical one, there is nevertheless also a central effect, less evident, but still unquestionable, that also other Authors noticed ([7]). E_2 does'nt modify, FSH undergo a reduction scarcely significant, with a stabilization between the fourth and twelfth month, whereas LH keeps on decreasing, more rapidly from the first to the fourth month than from the fourth to the twelfth one. Such course is difficult to explain and, in any case, it is not the object of our research.

S effect on non hirsute women's androgens, although they were administered even a double dose of it, is almost null: it almost seems the hypophysis-gonads-adrenals feed-back is less sensitive in normal than in hirsute women. T reduction can partly depend on the decreased LH secretion, seen in hirsute women but not in normal ones; T would electively respond to such secretion because it is higher than normal, while estrogens and progesterone, whose levels are initially within the normal limit, would not respond ([8]). This would explain the problems we had in regulating the menstrual cycles of the two oligomenorrhea cases presenting PCO: this kind of response is also slower in PCO cases than in idiopathic hirsutism ones.

There is a considerable amount of risk connected to such therapy, not as much for the woman than for a baby conceived during the drug-taking period. One year of therapy was necessary to obtain a 22% hair reduction; this provoked 26% LH gonadotropin reduction in comparison with its basal value. It is difficult to believe that this is not riskful for the fetus; besides, androgenic hormones reduction is dangerous for it.

It is impossible to say whether the results achieved during the treatment with S will last after its interruption. However, we saw that the therapeutic effect remains the same in spite of cyclic interruptions: following the advice of some Authors ([7]) we administered S for 21 consecutive days every month, and then suspended it for 9 days. Such administration probably reduced the number of possible therapy complications ([4, 13]).

If we take into consideration the overmentioned risks (mostly fetal) and the advantages of the therapy with S (22% hair reduction, a very little improvement), we come to the conclusion that in case of hirsutism, therapy with S should be considered:

– in case of failure of other kinds of therapy or when they cannot be applied;

– when a safe and suitable contraception is guaranteed to the woman, and is protracted for a few months after S suspension, as its androgenic action continues for some time.

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