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Effects of Sulpiride on Levels of FSH, LH and Steroid Hormones

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In order to study the effects of prolactin upon the gonadotrophins and steroid hormones, hyperprolactinaemia was induced by the administration of sulpiride. 12 men between the ages of 18 and 20 were given 3 capsules of 50 mg of sulpiride daily for a period of 15 days, and the following parameters being measured before and after the treatment: (prolactine, FSH, LH, testosterone, estradiol, ACTH and DHEA-S) by RIA, (cortisol) by fluorimetry and (etiocholanone, androsterone, pregnandiol, pregnantriol, pregnantriolone, 11-keto etiocholanone and 11-OH androsterone) by gas chromatography.

Our results show that on termination of the treatment there was a significant rise in the prolactin and DHEA-S serum levels and a drop in the FSH serum levels but not of LH. In addition there was a marked increase in all the androgen levels studied, (etiocholanone, androsterone and 11-keto etiocholanone) with the exception of testosterone.

Key words: Sulpiride, Gonadotrophins, Steroid hormones.

It is known that certain dysfunctions of the hypothalamopituitary gonadal axis are associated in both sexes with hyperprolactinaemia. Individuals with elevated prolactin levels in the blood have been found to suffer from amenorrhea (8, 11, 12), infertility (36), and impotence (26). These symptoms disappeared after treatment with a dopaminergic substance.

The mechanism responsible is not fully understood. The question is whether prolactin exerts a direct action on gonads due to direct impairment of the function of the corpus luteum (14, 33), estradiol and progesterone biosynthesis in the ovary (21, 29) the effects of LH on the Leydig cell (38, 39) or whether it acts indirectly, modifying the gonadotrophin levels in the blood (6, 30, 34).

In hyperprolactinemic women, however, hirsutim is not uncommon (24, 37, 40) and many studies have shown that in

many of these women, adrenal dihydroepiandrosterone and dihydroepiandrosterone sulfate secretion are increased (4, 15, 41, 42).

In order to study the effects of hyperprolactinaemia on the basal gonadotrophins and adrenal and gonadal steroid secretion, gonadotrophins and steroid hormones were measured in men before and after treatment with sulpiride.

Materials and Methods

A total of 12 healthy white male volunteers aged 18-20 which weighed 65 to 85 kg were studied. They were given 3 capsules of 50 mg of sulpiride daily for a period of 15 days.

20 ml of blood were drawn from volunteers under basal conditions, before and immediately after treatment. Studies were performed after overnight fact, starting at 09.00 h. After coagulation at room temperature, the samples were centrifuged at 400 g for 10 minutes to obtain serum which was then stored at —20° C until analyzed.

Twenty four hour urine was collected from each volunteers before and after treatment.

Sample analysis. Prolactin, FSH, LH, testosterone, estradiol, ACTH and DHEA-S serum levels were measured by RIA, using unmodified Cea-Ire-Sorin kits. The coefficients of variation inter-assay were 8,3; 5,5; 9,5; 5,6; 15; 25 and 9 % respectively. The cortisol blood concentrations were measured by fluorimetry using the MATTINGLY technique (28). The coefficient of variation inter assay was 4 %.

The suprarenal steroids were measured by gas-chromatography. The parameters measured were: etiocholanone, androsterone, pregnandiol, pregnantriol, pregnantriolone, 11-keto etiocholanone and 11-OH androstérone.

The results were analyzed statistically using paired Student's «t» test.

Results

Table I shows the serum levels of prolactin, FSH, LH, testosterone, estradiol, ACTH, cortisol and DHEA-S concentrations before and at the end of treatment with sulpiride. On termination of the treatment a marked increase in the prolactin ($p < 0.001$) and DHEA-S plasma levels ($p < 0.001$) and a significant drop in the FSH plasma levels ($p < 0.001$) were observed. Mean plasma LH, estradiol, testosterone, cortisol and ACTH were similar before and after treatment.

Table II shows the concentrations of different suprarenal steroids studied before and at the end of treatment with sulpiride. There was a marked rise in the etiocholanone ($p < 0.01$), androsterone ($p < 0.01$) and 11 keto-etiocholanone ($p < 0.01$) urine levels. Pregnandiol, pregnantriol, pregnantriolone and 11OH-androsterone mean urine levels were similar before and after treatment.

These observations were not associated with a significant decrease in basal levels LH after treatment. Although the mean values decreased 20 % (from 2.5 to 2 ng/ml), this is attributable to the great variability of the LH response after the treatment with sulpiride.

Discussion

These results coincide with those of other authors in showing a significant increase in PRL levels (table I) after

Table I. *Serum levels of different hormones studied before and after sulpiride administration.*
The data are expressed as mean ± S.E. The concentrations are expressed in pg/ml for estradiol and ACTH in μg/100 ml for cortisol, and in ng/ml for the other hormones.

Treatment	Prolactin n = 12	FSH n = 12	LH n = 12	Testosterone n = 12	Estradiol n = 12	ACTH n = 12	Cortisol n = 12	DHEA-S n = 6
Before	12.2 ± 1.2	2.2 ± 0.1	2.5 ± 0.2	4.7 ± 0.4	21 ± 1.4	33 ± 1.7	192 ± 20	4166 ± 461
After	57.0 ± 5.4***	1.8 ± 0.1***	2.0 ± 0.1	4.2 ± 0.3	20 ± 2.0	31 ± 1.8	193 ± 14	4760 ± 435***

***P < 0.001

Table II. *Urine levels of different steroid studied before and after sulpiride administration.*
The data are expressed as Mean ± S.E. The concentrations are expressed in mg/24 hours.

Treatment	Etiocholanone	Androsterone	Pregnandiol	Pregnantriol	Pregnantriolone	11keto-etiocholanone	11OH-androsterone
Before	2.6 ± 0.3	5.6 ± 0.6	1.7 ± 0.3	1.0 ± 0.2	0.8 ± 0.2	0.5 ± 0.1	0.7 ± 0.1
After	3.8 ± 0.4**	7.1 ± 0.8**	2.4 ± 0.4	1.1 ± 0.4	1.0 ± 0.4	0.8 ± 0.1**	0.8 ± 0.2

**P < 0.01

treatment with sulpiride (10, 20, 23, 27). This is to be expected since we are dealing with an antidopaminergic substance (7, 22).

This hyperprolactinaemia is associated with a noticeable drop in FSH serum levels but not of LH (table I). These findings are in accordance with studies using metoclopramide in postmenopausal women (1) and studies of patients with prolactin secreting pituitary adenomas (32). On the other hand, they do not agree with studies using metoclopramide in normal menstruating women (1) sulpiride in patients with Turner's syndrome of in women with hyperprolactinaemic amenorrhea (25).

It is noteworthy that the effect of hyperprolactinaemia is only on FSH serum levels and not on those of LH, as other authors have found (3, 16, 17, 19). This suggests that the action of prolactin on the gonadotrophins is not exerted through LH-RH, but a direct action on the pituitary cells. Hyperprolactinaemia results in increased storage of FSH by impairing its release (18). These findings might be also explained by the exaggerated gonadotrophin response especially of FSH to LH-RH in pathological (13, 35) or lactational hypersecretion of PRL (2, 9). Another possibility is that there is a neurotransmitter or some other hypothalamic regulating factor (stimulated by prolactin or sulpiride) which has a more specific control over FSH than LH.

Serum levels of testosterone and estradiol were similar before and after treatment with sulpiride. This is not in accordance with studies of VERMEULEN, *et al.* (40), who found low plasma testosterone levels in patients with a prolactinoma. This discrepancy could be explained by the brevity of treatment in our study. These findings suggest that hyperprolactinaemia lower FSH levels, through a direct effect not related to alterations in testosterone or estradiol secretion as ANDERSEN *et al.* (1) found in women.

The results obtained show that hyperprolactinaemia is associated with a significant increase in all the androgen levels studied (table II), with the exception of testosterone. Moreover, we have observed increased secretion of DHAS by the adrenal cortex. This finding agrees with those of BASSI *et al.* (4) and VERMEULEN *et al.* (4) but has not been confirmed by other authors (1, 5, 30). On the other hand, as the ACTH, cortisol (table I) pregnandiol, prenantriol and pregnantriolone do not vary (table II), we suggest that prolactin or another substance stimulated by sulpiride, acts directly upon the adrenals increasing only their androgenic production.

The drop in the FSH levels might be due to the increase in adrenal androgens, but it is unlikely since there was no effect on LH serum levels and since these adrenal androgens have very little androgenic action.

Resumen

Se estudia el efecto de la prolactina sobre los niveles de gonadotrofinas y hormonas sexuales mediante una hiperprolactinemia por administración de sulpiride. A 12 hombres de edad comprendida entre los 18 y 20 años se les administró 3 cápsulas diarias con 50 mg de sulpiride durante un período de 15 días y se midieron los siguientes parámetros antes y después del tratamiento: Prolactina, FSH, LH, Testosterona, Estradiol, ACTH y DHEA-S, por RIA (cortisol) por fluorimetría y (etiocolanona, androsterona, pregnandiol, pregnantriol, pregnantriolona, 11-ceto eticolanona y 11-OH androsterona), por cromatografía de gases.

Los resultados muestran que al final del tratamiento hay un aumento significativo de los niveles de prolactina y DHEA-S y una disminución significativa de los niveles de FSH, además de todos los andrógenos estudiados (etiocolanona, androsterona y 11-ceto etiocolanona) con excepción de la testosterona.

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