STEROID EXCRETION IN USERS OF THE INJECTABLE COMBINED OESTROGEN PROGESTOGEN PREPARATION, DELADROXATE*

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INTRODUCTION

Urinary steroid analysis in contraceptive pill users has been the subject of investigation by many authors. This was either to evaluate the pill as a good and reliable ovulation inhibition preparation, and this was achieved by pregnandiol assays, or by the latter together with oestrogen assays to reveal the ovarian functional activity under such treatment. Moreover, researches were directed towards the effect of steroid contraceptives on other steroid producing endocrine glands as the adrenals to examine to what extent these exogenous synthetic preparations affect the endogenous hormonal environment of the body. In a series of investigations the first author examined the effects of different types of steroid oral contraceptive combinations on the ovarian and adrenal activities in human and experimental animals. In this investigation, it was considered that steroid excretion analysis before and after the monthly injectable preparation, deladroxate, would be of value especially for comarative purposes.

MATERIAL & METHODS

Nine healthy fertile women of regular menstrual cycles aged 20—35 years, were selected for this study. None of them have family history of diabetes, endocrine, kidney or liver disease. They were not taking any other steroid contraceptive preparation for six months before this trial. In all treated cycles, injection was on the 8th day of the cycle.

* Deladroxate is 150 mg. of dihydroxyprogesterone acetophenide combined with 10 mg. of oestradiol enanthate per ml. of oily solution.

Twenty four hour urine collections were made on day 23 of the cycle, whether before or after injection. This date was chosen to represent pregnandiol peak and as well gives a good idea about the state of activity of the adrenal cortex as detected by 17-keto and 17-ketogenic steroids (17-KS & 17-KGS), besides giving an idea about oestrogen excretion post-treatment especially when compared with oestrogen excretion at the same day of the cycle before injection.

The urine was measured and samples were kept in the deep freeze for the assay of pregnandiol, oestriol, 17-KS, and 17-KGS. In all cases hormonal assays were done the same week of collection. Pregnandiol was measured according to the method of Klopper et al (1955), oestriol by a method slightly modified from that of Eberlein et al (1958), and the 17-KS and 17-KGS by the method of Norymberski et al (1953) as modified by Diczfalusy et al (1955). The Zimmerman reaction was performed using the organic base N-benzyl-trimethyl ammonium methoxide according to Bongiovanni et al (1957).

These analyses were repeated 3 and 6 months after the injection of deladroxate. We were able to follow up 6 cases for 3 months, and 5 of them for 6 months.

RESULTS

The results of the 24 hour urinary excretion of pregnandiol, oestriol, 17-keto and 17-ketogenic steroids before and after the injection of deladroxate are shown in table.

Pregnandiol determinations after 3 and 6 months of treatment show in all cases values below 1 mg/24 hrs, indicating anovulatory cycles.

As regards oestriol before injection, the mean urinary level was 18.05 mcg/24 hrs with a range of 12.0—18.64 mcg/24 hrs excluding one case who showed a relatively high value (37.26 mcg/24 hrs). After 3 monthly injections a significant decline in the oestriol levels was detected in the cases followed up. A similar decrease was also clear after 6 months. Mean values after 3 and 6 months were 13.02 and 7.23 mcg/24hrs respectively.

Results of the 17-ketosteroids show normal values for the cases examined before injection of deladroxate. After 3 months of treatment variable ranges of decline were detected in the cases followed up. Mean values showed a decrease from 11.05 before deladroxate to 6.5 and 5.0 mg/24hrs after 3 and 6 injections respectively.

Effect of Deladroxate on the Urinary excretion of Oestriol, Pregnandiol, 17 Keto and 17 Ketogenic Steroids

	Case Ns.	Oestriol (ug/24 hrs)	Pregnandiol (mg/24 hrs)	17-Ketosteroids (mg/24 hours)	17-Ketogenic steroids (mg/24 hrs
Before injection	9				
Mean		13.69	2.27	8.49	9.74
S. E.		0.662	0.23	0.847	0.93
After 3 monthly injections	6				
Mean		10.18	0.71	4.65	8.12
S. E.		2.08	0.09	0.78	1.04
After 6 monthly injections	5				
Mean		7.65	0.64	3.61	8.28
S. E.		1.44	0.28	0.4	0.57

17-ketogenic steroids show in general a tendency to decrease from a mean value of 8.66 before deladroxate to 6.67 mg/24hrs after 3 months the mean value was similar to that after 3 months of treatment (6.5 mg/24hrs).

DISCUSSION

In so far the endocrine control of ovulation in the human is concerned, the pituitary gonadotrophic hormones FSH and LH are mostly responsible for the growth and maturation of the graafian follicle as well as the regulation of the synthesis and release of the ovarian hormones oestrogens and progesterone. Ovulation is inhibited by either altering the rate at which the FSH and/or LH are secreted without affecting their total amount or by inhibiting their production to a certain extent. Some of the oral steroid contraceptives were found to abolish the peak of gonadotrophin excretion, especially of LH, which normally occurs with ovulatory menstrual cycles. Consequently, a detectable reduction in the ovarian hormones, oestrogens and

progeserone is expected to occur under such treatment. Therefore, urinary pregnandiol, the unique metabolite of progesterone, is taken as a good parameter for detecting ovulation. In this respect, it must be mentioned that other methods as basal temperature records, vaginal smears or endometrial biopsies are unsuitable in this case as synthetic progestogens may be thermogenic and the other methods may be similarly obscured. Urinary oestriol is also of great value in stating the functional activity of the ovaries under such treatment.

Pregnandiol determinations on day 23 of the cycle before injection of deladroxate revealed in this investigation, that all cases chosen for this study were ovulating and had levels of oestriol within the normal range at that particular time of the cycle. Results of pregnandiol obtained when using delatroxate for 3 and 6 months showed that deladroxate inhibits ovulation. Also a decrease in the level of urinary oestriol was detected after 3 months of treatment. After 6 months of treatment this decrease became more significant. Comparing these results with previous data obtained with other combined steroid contraceptive preparations, deladroxate is similar, from this particular point of view, to other combined preparations.

As regards the effect of deladroxate on the adrenocortical activity as detected by urinary 17-keto and 17-ketogenic steroids a decrease in the former after 3 months of treatment followed by another decrease after 6 months was found. However, it must be mentioned that inspite of this decrease, the values of 17-KS obtained, including those after 6 months are still on the borderline of the low normal levels for their ages.

The effect of deladroxate on the 17-ketogenic steroids showed a different pattern. A slight decrease was detected after treatment for 3 months from a mean value of 9.74 to 8.74 mg/24 hrs. The latter value was nearly similar to that obtained after 6 months of treatment. Similar results concerning the effects of oral steriod contraceptives on 17-KS and 17-KGS were obtained by other investigators. Starup et al (1966), studying the adrenal function during oral contraception treatment with megestrol acetate plus mestranol preparation (Delpregnin), they stated that 17-KGS were decreased in the 1st month and remained at the lower level of normal limits. 17-KS decreased more markedly and half of the values remained below normal. Ostergaard *et al* (1966), studying the same preparation stated that 17-KGS fell slightly

in all cases. Mestman *et al* (1967), reported a significant decrease in baseline of 17-KGS and 17-KS during norinyl therapy (norithisterone combined with mestranol).

That 17-KS are more affected in this investigation than 17-KGS is to be expected. The sources of 17-KS in human are mainly the adrenals, the metablism of 17-OHCS and a small portion from the ovaries. So one can say that the slow metabolic rates of 17-OHCS reported under such combined treatment, the slight suppression of adrenocortical activity and the marked suppression of ovarian activity were collectively addetive factors responsible for the low 17-KS levels detected in thes cases.

The slight decrease in 17-KGS must not be taken as indication of low adrenocortical functional reserve capacity. ACTH stimulation test for the adrenal cortex was found to remain unchanged in pill users (Richter, 1963 ; Wallack *et al*, 1963). Gontermann and Oertel (1966) and Givens *et al* (1968) stated that the reduction in corticosteroid excretion and the elevation of plasma 17-OHCS they found in subjects treated with the combined oestrogen progestogen preparations are mainly due to the increased binding capacity of the plasma proteins caused by the oestrogen component of the preparation.

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