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Unaltered Lipoprotein and Carbohydrate Metabolism during Treatment with Contraceptive Subdermal Implants Containing ST-1435

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ABSTRACT

Nine healthy, fertile women were treated for six months with subdermal contraceptive implants of two different sizes containing a potent progestogen, ST-1435. Lipoprotein cholesterol and triglyceride concentrations were not influenced by the treatment. Similarly, the main apolipoproteins in low- and high-density lipoproteins were not changed, which further supports the interpretation that the lipoprotein metabolism is not affected by this type of treatment. An oral glucose tolerance test (OGTT) including insulin determinations was performed in five of the volunteers with the largest implants. Blood glucose and insulin concentrations during the OGTT remained unchanged during treatment, indicating that the treatment with ST-1435 did not affect carbohydrate metabolism.

INTRODUCTION

Epidemiologic studies have implicated significant relationships between coronary heart disease and certain types of lipoprotein patterns (6,13). A low concentration of high-density lipoproteins (HDL) is associated with an increased risk of coronary heart disease (6,13). Use of oral contraceptives has been shown to be a risk factor for the development of coronary heart disease (15). Therefore, several studies have, in recent years, dealt with the effects on the lipoproteins by different hormonal contraceptive combinations (2, 3, 8, 9, 11). It has thus been established that treatment with progestogens derived from 19-nortestosterone is associated with a decrease of the HDL-cholesterol levels (2, 3, 8, 9, 11). Investigations concerning the effects on the lipoprotein patterns by other progestogens are therefore essential and the development of compounds without such effects are of great interest.

The present study deals with a new progestogen, ST-1435 (16-methylene-17α--acetoxy-19-nor-4-pregnen-3,20-dione), which has been reported to have a very high contraceptive potency and no androgenic activities (4, 10, 12). Because of a very rapid metabolism and poor absorption from the gastrointestinal tract this progestogen has virtually no effect by the oral route of administration, whereas it has been shown to be highly active by the parenteral route (4, 10, 12).

MATERIAL AND METHODS

Design of the study

Silastic® capsules containing ST-1435 were used. They had a length of 7.5 mm and 30 mm, respectively, and an outer diameter of 2.4 mm. One 7.5 mm capsule was inserted subcutaneously in each of three women and two 7.5 mm capsules in one woman. Five women had one 30 mm capsule each. The daily release of ST-1435 was calculated by determination of the weight loss of steroid in the implants during treatment divided by the number of days the implants had been inserted. Thus the average daily release of ST-1435 from one 7.5 mm implant was calculated to be 30 μg and from one 30 mm implant 120 μg.

The volunteers were healthy, regularly menstruating women, 25-35 years old. They had been on no hormonal or other medication for several months before the study. The capsules were inserted in the left ventral forearm on the fifth day of a normal menstruation and left in place for six months and were then removed.

Before insertion an oral glucose tolerance test was performed. The test was repeated after one and six months of treatment. Blood samples for lipoprotein determinations were obtained just prior to insertion and then after one and six months of treatment. Blood samples were also obtained once or twice weekly before and during treatment to monitor effects on ovulations by determinations of progesterone, estradiol and ST-1435 concentrations.

Analyses of serum lipids, lipoprotein lipids and serum apolipoproteins

The serum triglyceride and cholesterol concentrations were determined in an isopropanol extract by semiautomatic methods in a Technicon Auto Analyzer type II in whole serum and in the top, corresponding to the very-low-density lipoproteins (VLDL), and in the bottom fractions after preparative ultracentrifugation at density 1.006. The low-density lipoproteins (LDL) were precipi-

tated from the bottom fraction, using a heparin-manganese chloride solution and the HDL concentrations were determined in the supernatant.

The concentrations of the apolipoproteins B, A-I and A-II in whole serum were determined by a rocket immunoelectrophoresis technique using the concentrations in a pooled serum as a reference given the value 100 per cent. The concentrations are thus expressed in arbitrary units (AU). The methods have been reported in detail elsewhere (17).

Oral glucose tolerance test (OGTT)

An OGTT was performed giving 100 g glucose in 200 ml water solution. Blood samples for glucose and insulin determinations were taken before and after 30, 60, 90 and 120 minutes.

Statistics

Means and standard errors were calculated by ordinary methods. Two groups of volunteers were considered, users of 7.5 mm (1 or 2) and 30 mm implants. A linear crossed nested model including the main factors, groups and time points, their interaction and the factor "patient nested within group" was used for the statistical analysis. This model provides better means to estimate error terms, increases the degree of freedom for the error terms compared with calculations performed in each group separately, which improves the power to discover treatment effects despite the small number of patients in each group. Contrasts in the interaction were tested in order to find differences between the effects of the treatment.

RESULTS

All the pretreatment cycles were ovulatory as judged by estradiol and progesterone concentrations in plasma. Eight of the women were anovulatory throughout treatment. In one woman with a single 7.5 mm implant an ovulatory cycle was recorded during the sixth month of treatment.

Treatment with ST-1435 implants did not cause any significant changes of cholesterol or triglycerides in any of the lipoprotein classes. Furthermore, the concentrations of the apolipoprotein B (main constituent of LDL) and A-I and A-II (main protein constituents of HDL) were not affected by the treatment. Thus the estimated lipid/protein composition of LDL and HDL remained constant.

The lipoprotein lipid and serum apolipoprotein concentrations were analyzed in both groups of volunteers (7.5 mm and 30 mm). In the statistical analysis the effects in the two groups were considered separately. There were no significant differences in any respect between the groups with regard to response to treatment. Furthermore, there were no obvious trends indicating a more pronounced effect after one month than after six months. Therefore, the mean values for all subjects, irrespective of treatment with 7.5 mm or 30 mm implants, are presented in Table 1.

Table 1. Mean (SEM) concentrations of triglycerides (tg) and cholesterol (chol) in very-low-density (VLDL), low-density (LDL) and high-density (HDL) lipoproteins and in total serum (mmol/l) and apolipoproteins (Apo) B, A-I, A-II (arbitrary units) before treatment and after one and six months of treatment with subdermal implants containing ST-1435.

	Before	One month	Six months
VLDL tg	0.36 ± 0.11	0.38 ± 0.12	0.35 ± 0.14
VLDL chol	0.17 ± 0.05	0.17 ± 0.08	0.14 ± 0.10
LDL tg	0.37 ± 0.05	0.36 ± 0.06	0.33 ± 0.08
LDL chol	2.62 ± 0.71	2.76 ± 0.83	2.63 ± 0.72
HDL tg	0.19 ± 0.07	0.23 ± 0.02	0.24 ± 0.33
HDL chol	1.42 ± 0.28	1.39 ± 0.26	1.40 ± 0.33
Serum tg	1.03 ± 0.33	0.98 ± 0.18	0.91 ± 0.13
Serum chol	4.23 ± 0.84	4.32 ± 0.88	4.27 ± 0.79
Apo B	87.2 ±19.7	93.6 ±20.1	91.1 ±19.1
Apo A-I	92.7 ± 8.8	95.4 ±10.1	97.8 ±12.2
Apo A-II	89.9 ± 7.8	94.7 ±14.4	93.3 ±10.3

The five women treated with 30 mm implants were also studied with regard to glucose metabolism. The mean values at the different time points during the OGTT are given in Table 2, as are those for body weight. One volunteer, previously overweight, increased 5.8 kg during treatment which was accompanied by higher insulin values at the six months OGTT. This explains the tendency for higher average insulin values to be found on this test occasion. However, all average changes in blood glucose, insulin and body weight were statistically non-significant.

Table 2. Mean (SEM) body weight (kg) and insulin concentrations (mU/l) and glucose concentrations (mmol/l) during an oral glucose tolerance test performed before and after one and six months of treatment with subdermal implants containing ST-1435.

	Before	One month	Six months
Body weight	63.9 ± 9.2	63.5 ± 7.4	65.5 ±10.6
Insulin 0 min	8.1 ± 3.0	8.3 ± 3.1	9.5 ± 1.3
Insulin 30 min	42.6 ±11.4	47.0 ±26.7	49.5 ±27.5
Insulin 60 min	38.8 ±12.4	42.3 ±25.4	44.6 ±11.6
Insulin 90 min	30.9 ± 7.3	29.2 ±13.1	36.6 ± 5.4
Insulin 120 min	20.9 ± 7.3	29.6 ±10.8	25.8 ± 5.9
Glucose 0 min	4.9 ± 0.5	4.6 ± 0.5	4.8 ± 0.4
Glucose 30 min	6.9 ± 1.6	6.4 ± 0.9	7.3 ± 1.9
Glucose 60 min	5.5 ± 2.5	4.8 ± 0.5	6.0 ± 3.7
Glucose 90 min	4.2 ± 1.1	4.1 ± 0.6	5.2 ± 2.0
Glucose 120 min	3.5 ± 0.7	3.5 ± 0.6	4.5 ± 1.2

DISCUSSION

An implant method for contraception should aim at ovulation suppression in order to provide efficacy and safety. A sustained release system offers contraceptive efficacy for a prolonged period with a comparatively low dose of the progestogen, thus avoiding unwanted effects associated with higher doses.

Although the present study deals with a limited number of volunteers the results are promising since ST-1435 proved efficient in ovulation inhibition without causing any changes in the lipoprotein patterns nor in carbohydrate metabolism.

The calculations of the release rate of ST-1435 were made under the assumption that the release is even throughout treatment. However, previous studies have shown that the release of progestogen from capsules is in fact higher at the beginning of treatment (14), which was also reflected by decreasing plasma concentrations of ST-1435 throughout treatment (12). The results obtained after one month would therefore have been expected to deviate from the other treatment results had there been a clearly dose dependent effect on the lipoproteins by the progestogen. Moreover, the results in the women with

30 mm implants did not differ from those of the women with only a 7.5 mm implant, suggesting that there is no dose dependency, at least within the dose range used in the present study.

Levonorgestrel used for continuous release from contraceptive vaginal rings has been shown to lower HDL-cholesterol by about 25 per cent when the calculated daily release of levonorgestrel was 300 μg (2). Women treated for three years with subcutaneous implants releasing about 30 μg levonorgestrel daily had significantly lower levels of total cholesterol, triglycerides and LDL-cholesterol but the same level of HDL-cholesterol as untreated controls (5). Depression of HDL-cholesterol has also been reported during treatment with progestogen-only oral formulations of norethindrone (3) and lynestrenol (8). The effect on HDL-cholesterol by the 19-nortestosterone derived progestogens is obviously dose dependent and could be attributed to an androgenic potency of these hormones. ST-1435, although its chemical structure relates to that of the 19-nortestosterone derived progestogens, seems to relate more to progesterone in its clinical and biochemical properties. Thus, ST 1435 lacks androgenic effects as reflected by lack of affinity to sex hormone binding globulin (SHBG), nor does it affect SHBG binding capacity in plasma (7).

Several investigators have reported that combined oral contraceptives are associated with a deterioration in glucose tolerance, whereas comparatively few have studied the effects on carbohydrate metabolism by progestogen-only preparations. Spellacy et al (16) reported significant increases in plasma insulin and deterioration in 15% of the glucose tolerance curves in women treated with 75 μg norgestrel per day orally. Åhrén et al. (1) found unchanged fasting glucose and insulin concentrations in plasma in 22 women treated with a contraceptive vaginal ring releasing 300 μg levonorgestrel daily. They reported, however, a significant increase in peak insulin after an intravenous glucose tolerance test compared to pretreatment values. The glucose half-life did not change during treatment with the levonorgestrel ring. These findings did not suggest any changes in peripheral insulin sensitivity but rather an increase in the sensitivity of pancreas to the glucose load (13).

In conclusion, this study has shown that by using a very low dose of ST-1435 continuously released from a subcutaneous implant, contraceptive efficacy was achieved for six months without any effects on lipoprotein or apolipoprotein concentrations, nor on glucose metabolism. These findings, together with the lack of effect by the oral route, could make ST-1435 a very suitable contraceptive for implant use. By manipulating the Silastic capsule it

would be possible to achieve contraceptive efficacy for a longer period than six months, ideally one to two years with only a single implant.

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