Effects of a new oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, on the renin-aldosterone system, body weight, blood pressure, glucose tolerance, and lipid metabolism

W Oelkers, JM Foidart, N Dombrovicz, A Welter and R Heithecker

Effects of a New Oral Contraceptive Containing an Antimineralocorticoid Progestogen, Drospirenone, on the Renin-Aldosterone System, Body Weight, Blood Pressure, Glucose Tolerance, and Lipid Metabolism

W. OELKERS, J. M. FOIDART, N. DOMBROVICZ, A. WELTER, AND R. HEITHECKER

Division of Endocrinology, Klinikum Benjamin Franklin (Steglitz), Freie Universität (W.O.), and Fertility Control, Schering AG (R.H.), Berlin, Germany; Catholique Hôpital Universitaire Liege (Sart Tilman) (J.M.F., N.D.), and Laboratoire du Vieux Mayeur (A.W.), Liege, Belgium

Abstract

Combined hormonal oral contraceptives (OCs) may lead to a mild rise in blood pressure and body weight. In rare instances, large increments in blood pressure are measured. We investigated the effect of a combination of ethinyl estradiol (EE) plus a progestogen with antimineralocorticoid, i.e., natriuretic, properties (Drospirenone (DRSP)) on body weight, blood pressure, the renin-aldosterone system, atrial natriuretic factor, plasma lipids, and glucose tolerance. It is anticipated that this will lead to the development of an OC that does not raise body weight or blood pressure.

Four groups of 20 women each received 30 μg EE plus 3 mg DRSP (group A), 20 μg EE plus 3 mg DRSP (group B), 15 μg EE plus 3 mg DRSP (group C), and a control OC: 30 μg EE plus 150 μg levonorgestrel (Microgynon, Schering; group D) for 6 months.

During the OC-free control cycles before and after treatment and throughout treatment, the target parameters were measured. Between the pretreatment cycle and the sixth treatment cycle, mean body weight fell by 0.8 to 1.7 kg in groups A, B, and C (P < 0.05 vs. D), whereas it rose by 0.7 kg in group D. Systolic and diastolic blood pressures fell by 1–4 mm Hg in groups A, B, and C (significant for A and C vs. D) and increased by 1–2 mm Hg in group D. Renin substrate rose equally in all groups (P < 0.05), whereas PRA and plasma aldosterone rose significantly only in the DRSP groups, presumably due to sodium loss. In the DRSP groups, high density lipoprotein cholesterol rose (P < 0.05), in contrast to group D. Low density lipoprotein cholesterol fell slightly (P > 0.05), whereas triglyceride levels showed a stronger increase in the DRSP groups (P < 0.05) than in group D. All groups attained good cycle control; group A had the best. Side-effects were minimal. To our knowledge, this is the first report on a combined OC that leads to a small decrease in body weight and blood pressure. It may be especially beneficial for women susceptible for a gain in weight and a rise in blood pressure. (J Clin Endocrinol Metab 80: 1816–1821, 1995)

Prolonged use of hormonal oral contraceptives (OC) containing an estrogen and a progestogen may lead to slight mean increases in body weight and blood pressure (1–3). In this regard, there is no significant difference among various preparations containing 50 or 30 μg ethinyl estradiol (EE) (4). In rare instances, OC use may lead to severe or “malignant” hypertension (5–7). The estrogenic compound in an OC usually causes a slight elevation in the plasma concentrations of high density lipoproteins (HDL), a change believed to reduce the risk of atherosclerosis (8, 9). If progestogenic compounds of an OC are derivatives of 19-nor-testosterone, however, it may counteract this potentially favorable effect of the estrogen. Some combined OCs containing such progestogens may even lead to a slight fall in the HDL cholesterol level (8, 9). Most of the modern low dose progestogens in OCs are 19-nor-testosterone derivatives.

We recently reported on a new progestogen with antimineralocorticoid activity, which suppresses ovulation in most normally menstruating women in a daily dosage of 2 mg. Drospirenone (DRSP), formerly called dihydrospironorenone, is chemically related to 17α-spironolactone, with about 8 times its antimineralocorticoid activity in man (10). Here we report on the first long term trial conducted in young female volunteers with OCs containing variable dosages of EE and 3 mg DRSP. The study was designed to investigate changes in the renin-aldosterone system. Body weight, blood pressure, plasma lipids, and glucose tolerance were of further interest. It was expected that an OC containing a progestogen with such properties would not lead to an increase in body weight or blood pressure.

Subjects and Methods

Trial protocol and subjects

Eighty healthy women, between 18–34 yr of age, were included in the study. Smokers (up to 10 cigarettes/day) had to be younger than 30 yr. Previous OC users (61% of women altogether, no significant difference between groups) had to observe a wash-out period of 1 month before the control (pretreatment) cycle of the present study. Apart from advising the women to avoid large amounts of salt in their diet, no attempts were made to control the diet in this long term trial. All participants gave written informed consent to the study protocol, which had been approved by the ethics committee of the Berliner Arztekammer (Chamber of Physicians of Berlin). The duration of the trial was 8 months (1 OC-free

Received January 20, 1994. Revision received November 29, 1994. Accepted February 8, 1995.

Address all correspondence and requests for reprints to: Wolfgang Oelkers, M.D., Abteilung Freien Universität Berlin Endokrinologie, Klinikum Steglitz der FUB, Hindenburgdamm 30, 12200 Berlin, Germany.
pre-treatment cycle, 6 treatment cycles, and 1 OC-free post-treatment cycle. According to a randomization list, each of 80 women was assigned to 1 of the following 4 treatment groups of equal size: group A, 3 mg DRSP and 30 μg EE; group B, 3 mg DRSP and 20 μg EE; group C, 3 mg DRSP and 15 μg EE; and group D, 0.15 mg levonorgestrel and 30 μg EE (Microgynon, Schering, Berlin, Germany).

In a previous study, the threshold dose of DRSP for the inhibition of ovulation was found to be 2 mg/day (10). To provide a safety margin for clinical use, the dose of 3 mg DRSP was chosen. Three different dosages of EE were chosen to gain information on an estrogen dose effect on the various parameters measured and on cycle control.

The drugs were taken from days 1-21 of the treatment cycles, followed by a pill-free interval of 7 days. Each subject had to keep a bleeding diary and was asked at each visit about the course of her cycle and her general well-being throughout the study.

All persons involved in the trial, including those performing laboratory analyses, were unaware of the treatment group to which a volunteer belonged. Primary target variables of the present study were effects of the OC preparations on the factors of the renin-aldosterone system. Secondary variables were effects on well-being, cycle control, body weight, blood pressure, serum electrolytes and creatinine, plasma atrial natriuretic factor (ANF) and lipids, and glucose tolerance.

**Methods of measurement**

Body weight was measured by the women themselves every second day throughout the trial on home scales, unclothed, and in the fasting state. Measurements were entered into weight charts that had been given to each woman. Average weights during a cycle were used for calculations.

Blood pressure was measured using an electronic Speidel-Heller (5k) meter (ungingen, Germany) on the 21st day of each cycle of the trial after at least 5 min in the sitting position. The mean of three subsequent measurements, at least 2 min apart, was used for further calculations.

Blood for measuring the components of the renin-aldosterone system was collected on days 5 and 21 of the pretreatment cycle and then on day 21 of treatment cycles 1, 3, and 6. An oral glucose tolerance test (100 g glucose; blood glucose measured at 0, 60, 120, and 180 min) was carried out on day 21 of the pretreatment cycle and the sixth treatment cycle. The metabolic parameters glucose, triglycerides (13), and total cholesterol were determined enzymatically; HDL cholesterol was measured after appropriate precipitation reaction. LDL cholesterol was calculated using Friedewald’s formula (14). Analyses were performed using a Hitachi 704 or 705 autoanalyzer (Boehringer), based on standard procedures.

**Statistical methods**

The influence of the treatments on the respective parameters after six cycles was analyzed by comparing groups A, B, and C to the reference group D using two-sided Dunnett’s test. The significance level α was equal to 5%. An α-correction with respect to the number of parameters was not performed. The tests were performed on the basis of individual changes (observed value in the sixth treatment cycle minus observed value in the pre-cycle) to reduce variability between subjects.

Further statistical analyses of the respective parameters were performed. The homogeneity of the groups at baseline (pretreatment cycle) was tested with a one-way analysis of variance. The alteration of a parameter under treatment was analyzed for each group. For this purpose, the two-sided t test for dependent samples was used to compare the means in the pretreatment cycle and the sixth treatment cycle. The dependency between the individual changes in body weight and blood pressure (systolic and diastolic) between the pretreatment cycle and the sixth treatment cycle was evaluated with Pearson’s coefficient of correlation per group. Each correlation coefficient was tested to determine whether it was equal to zero. Each of these tests was also performed at a significance level of α = 5%. Again, α was not corrected with respect to the number of parameters or the number of comparisons. The computations were performed with the statistical analysis system SAS/Release 6.08 (SAS Institute, Cary, NC).

**Fig. 1.** Mean changes (Δ) in body weight (±SEM) and in systolic and diastolic blood pressure during treatment and in the posttreatment cycle in the DRSP groups (A, B, and C) and the control group D. At 6 months, weight changes in groups A, B, and C; changes in systolic blood pressure in group C; and changes in diastolic blood pressure in groups A and C were significantly different from those in group D.
Results

Body weight

Mean baseline body weight in groups A through D ranged between 57.9–62.0 kg. Differences were not significant. As shown in Fig. 1, mean body weight fell in groups A, B, and C from the pretreatment level until the sixth treatment cycle by 0.78, 0.68, and 1.66 kg, respectively, whereas it rose in group D (Microgynon) by 0.68 kg. The differences in weight changes between groups A, B, and C vs. group D were significant. A weight gain of greater than 2 kg occurred in none of the women of groups A and B, in one woman of group C, and in two women of group D. A weight loss greater than 2 kg occurred in one subject each in groups A and B, in six subjects in group C, and in no subject in group D. Mean weights in the posttreatment cycle had not yet reached those in the pretreatment cycle.

Blood pressure

Mean baseline blood pressure (control cycle) ranged between 112.7–118.1 mm Hg (systolic) and between 70.8–75.6 mm Hg (diastolic) in groups A, B, C, and D. Differences were not significant between groups.

Mean changes in systolic and diastolic blood pressure are shown in Fig. 1. Between the pretreatment and the sixth treatment cycles, systolic blood pressure fell in groups A, B, and C by 2.4, 0.9, and 4.4 mm Hg, respectively, whereas it increased in group D by 1.1 mm Hg. The respective changes in diastolic blood pressure were -3.4 mm Hg (group A), -2.3 mm Hg (group B), -4.1 mm Hg (group C), and +1.8 mm Hg (group D). The change in systolic pressure in group C and the changes in diastolic pressures in groups A and C were significantly different from the corresponding changes in group D. A significant correlation between the individual changes in body weight and blood pressure was not found.

PRS

Mean PRS levels in the different groups on day 21 of the pretreatment cycle ranged between 0.80–0.97 μmol angiotensin I equivalents/L plasma. Differences between groups were not significant. As shown in Fig. 2, PRS increased significantly during the treatment cycles, but the alterations in groups A, B, and C were not significantly different from those in group D and, therefore, were independent of the dose of EE (between 15–30 μg/day).

PRA

Mean PRA levels in the different groups on day 21 of the pretreatment cycle ranged between 0.93–1.2 ng/L-s. Differences between groups were not significant.

In the Microgynon group D, mean PRA did not change significantly between the pretreatment cycle and any of the treatment cycles, as shown in Fig. 2. PRA rose significantly in all groups taking DRSP as the progestogen after one cycle of treatment. Thereafter, PRA tended to decline in the DRSP groups. Only the changes in group A differed significantly from those in group D in the sixth month of treatment.

Plasma Aldosterone

Mean aldosterone levels ranged between 0.59–0.83 nmol/L at baseline, with no significant differences between groups. Aldosterone did not change significantly in group D, whereas it increased significantly in groups A, B, and C (Fig. 2). The changes in aldosterone in groups A, B, and C were significantly different from those in group D in the sixth treatment cycle.

Plasma ANF, electrolytes, and creatinine

ANF rose significantly in all groups independent of the dose of EE or progestogen, from 3.64 to 4.51 pmol/L in group A, from 3.51 to 4.45 pmol/L in group B, from 3.54 to 4.58 pmol/L in group C, and from 3.41 to 4.51 pmol/L in group
D. Increments in ANF during treatment were not significantly different between groups.

The mean serum sodium level was about 141 mmol/L, and serum potassium was approximately 4.1 mmol/L in the four groups, without significant changes during treatment.

Mean serum creatinine ranged between 89–93 µmol/L at baseline. Significant increments by 3.5, 7.0, 5.3, and 8.4 µmol/L in groups A, B, C, and D were found, but the increases in the DRSP groups were not significantly different from those in group D.

Serum lipids

Mean serum triglyceride levels in the pretreatment cycle were significantly higher in group D (1.1 mmol/L) than in DRSP groups A, B, and C (0.79, 0.71, and 0.71 mmol/L, respectively). For total, HDL, and LDL cholesterol, no significant differences between groups were found at baseline. Serum triglyceride levels rose in groups A, B, and C (47%, 73%, and 60%, respectively), whereas they did not change in group D (Microgynon). HDL cholesterol rose in groups A, B, and C by 9%, 23%, and 17%, respectively, whereas it fell by 12% in group D. The differences in triglycerides and HDL cholesterol between groups A, B, and C vs. group D were significant. LDL cholesterol fell in groups A, B, and C by 15%, 14%, and 20%, whereas it remained unchanged in group D. These differences between groups A, B, and C and group D were not significant (Fig. 3).

Glucose tolerance

Basal serum glucose remained essentially unchanged in all four groups. The results of the oral glucose tolerance test are expressed as the area under the curve for the 3-h test (grams per L/h). In group A, the area under the curve rose numerically between pretreatment and the sixth treatment cycle from 2.56 to 3.05 (19%), in group B from 2.58 to 2.95 (14%), in group C from 2.57 to 2.83 (10%), and in group D (Microgynon) from 2.64 to 3.02 g/L-h (14%). The differences between groups at baseline were not significant. The increases were significant in all groups, but those in groups A, B, and C were not significantly different from those in group D.

Cycle control and tolerance

Cycle control was good during treatment with all preparations, but, bearing in mind the relatively small number of cases, was best in group A. All trial preparations were well tolerated, both subjectively and objectively. Overall, symptoms of headache and breast tenderness were reported most frequently, more so in group D than in the DRSP groups.

Discussion

The suspicion that current use of OCs may lead to a rise in cardiovascular morbidity events has not been definitely substantiated by meta-analyses of epidemiological studies, except for deep vein thrombosis and pulmonary embolism (15-17). Nevertheless, the study of the Royal College of General Practitioners (18) found a significantly elevated risk of cardiovascular death associated with OC use, although with the high dose preparations (50 µg EE or higher) of 25 yr ago. As OCs are among the most widely used drugs, safety standards have to be extremely rigorous. If current use of OCs should lead to an increased incidence of cardiovascular disease, thromboembolism, and cerebrovascular accidents, then changes in blood pressure, plasma lipids, carbohydrate metabolism, and blood coagulation/fibrinolysis would be candidates as mediating factors. As past use of OCs, even prolonged, is not associated with an increased cardiovascular morbidity or death (19), it is unlikely that OCs favor the development of irreversible atherosclerosis, although some preparations may lead to increases in LDL cholesterol and a decrease in HDL cholesterol (8).

In the present study, we observed a very slight increase in systolic and diastolic blood pressure after 6 months use of treatment with 30 µg EE plus 150 µg levonorgestrel in group
D, similar to a WHO trial in which 30 or 50 µg EE plus 250 µg levonorgestrel were used (3). In a recent study by Nichols et al. (20), OCs containing 30 µg EE and four different progestogens (150 µg desogestrel, 75 µg gestodene, 150 µg levonorgestrel, and 1 mg norethisterone acetate) significantly increased systolic and diastolic blood pressure within 6 months of treatment, more so than in our group D or in the WHO trial (3). There was no difference between the "old" progestogen norethisterone acetate and the "low dose" progestogens desogestrel, gestodene, and levonorgestrel (20).

In groups A, B, and C (EE plus DRSP) of the present study, blood pressure fell slightly, similar to the control group in the WHO study, which was made up of a large number of women using intrauterine contraceptive devices (3). It is likely that the statistical power of our study (n = 20 for each group) was not great enough to confirm in all groups of DRSP-containing OCs an effect on blood pressure, which was not the main target of this trial. Nevertheless, this is, to our knowledge, the first observation of a fall in blood pressure in women taking combined OCs over 6 months, suggesting that DRSP in combination with EE slightly lowers blood pressure or prevents the increase observed with other combined OCs. The coincidence with a slight fall in body weight, in contrast to a slight increase in group D, suggests that the difference in blood pressure between the DRSP groups and group D is due to a decrease in extracellular volume. Other findings support this view.

In a previous study, we have shown that administration of 2 mg DRSP daily for 6 days to young women leads to a cumulative negative sodium balance of about 85 mmol compared with the effect of a placebo (10). This sodium loss was similar to that observed in young males who had been treated with progesterone injections or suppositories for 6 days (79 mmol cumulatively) (21). It is, therefore, reasonable to attribute the slight weight loss in the present study to the demonstrated antimineralocorticoid effect (10) of DRSP.

All contraceptive preparations used in our study led to the well known EE-induced increase in PRS. It is remarkable that a dose of 15 µg EE/day (group C) led to the same increase in PRS as 30 µg EE/day (groups A and D). Changes in PRA and aldosterone, however, were markedly different between the DRSP groups, on the one hand, and group D on the other. With levonorgestrel as the progestogen, PRA and aldosterone did not change, probably due to a compensatory fall in the active plasma renin concentration, as observed by Beckerhoff et al. (22) and Derkx et al. (23) in patients taking conventional combined OCs. In the DRSP groups, however, the presumed sodium loss induced by the antimineralocorticoid progestogen must have prevented the fall in active renin at least in part, as indicated by increases in PRA and aldosterone. The fact that blood pressure fell slightly instead of rising, in the presence of an increase in renin, is further evidence of mild sodium depletion, because the latter blunts the vascular effects of angiotensin II (24). Thus, the rise in PRA and aldosterone in groups A, B, and C seems to be a compensatory, not a hypertensiogenic, mechanism.

We would have expected changes in body sodium to be reflected by changes in plasma ANF in group D and the DRSP groups, because ANF falls after sodium deprivation and rises after sodium loading (12). However, differences between the DRSP groups and group D did not occur. ANF rose slightly and significantly between the pretreatment and the sixth treatment cycle in all groups due to unknown mechanisms. A rise in plasma ANF during OC use has been observed previously (25).

Changes in plasma lipids after treatment with DRSP-containing contraceptives with regard to triglycerides and HDL cholesterol are similar to those observed with preparations containing 30 µg EE plus desogestrel, gestodene, or cyproterone acetate, as summarized by Gaspard (9) in longitudinal studies and by Godsland et al. (8) in cross-sectional studies. The small decrease in LDL cholesterol observed in the three DRSP groups was rarely found with other contraceptives, apart from a cross-sectional study (8) that showed significantly lowered LDL cholesterol in women taking EE plus either desogestrel or low dose norethisterone. Whatever plasma lipid changes under OC treatment mean, the changes observed in the DRSP groups point in the "no atherogenic" direction.

Impairment of glucose tolerance is seen with all combined OCs (8, 26), although in a dose-dependent manner (27). Compared with increases in the area under the glucose curve in the OGTT by all monophasic combined OCs studied by Godsland et al. (8), impairment of glucose tolerance was moderate in the DRSP-containing OCs of our present trial.

In conclusion, combination OCs containing EE and DRSP are remarkable in their ability to slightly lower body weight and blood pressure. Cycle control was very good, especially in group A (30 µg EE and 3 mg DRSP), and the volunteers complained of few side-effects. The DRSP combinations have a favorable metabolic profile with regard to plasma lipids and glucose tolerance. It is, therefore, conceivable that a combination OC of this new type of progestogen may be of special benefit for women susceptible to weight gain and a rise in blood pressure.

References

COMBINED OC THAT DECREASES BW AND BLOOD PRESSURE


**ABIM Announcement Regarding Board Eligibility**

The American Board of Internal Medicine is planning to undertake a complete review of its policies concerning Board Eligibility. The ABIM anticipates that revised Board Eligibility policies will be announced by December 31, 1996.

In the interim, the rules concerning the duration and reestablishment of the Board Eligible status will be suspended. All candidates with this status will continue to be regarded as Board Eligible and therefore able to sit for the Certifying Examinations in internal medicine or the subspecialties. However, the Board's Qualifying Examination, developed to reestablish Board Eligibility, will not be offered.

Candidates who have questions about this policy should contact the American Board of Internal Medicine, 3624 Market Street, Philadelphia, PA 19104-2675 (1-800-441-2246).