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Prospective measurement of blood pressure and heart rate over 24 h in women using combined oral contraceptives with estradiol☆,☆☆

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Abstract

Objective: Combined oral contraceptives (COCs) containing ethinyl-estradiol are known to increase blood pressure (BP). We evaluated whether COCs containing estradiol (E2) influence 24-h ambulatory BP and heart rate (HR) in normotensive and normal-weight women.
Study design: Twenty-four-hour BP and HR were measured every 30 min with an ambulatory BP device in 18 normotensive healthy non-smoking women prior to (Days 3–6 of menstrual cycle) and after 6 months of use (Days 20–24 of cycle 6) of a COC containing either a quadriphasic combination of E2 valerate plus dienogest (n=11) or a monophasic association of micronized E2 plus nomegestrol acetate (n=7).
Results: Mean age and body mass index of the final sample were 32.50±7.49 years and 22.87±4.08, respectively. E2-based COCs induced no modification of 24-h systolic BP (+1.65±8.34 mmHg; p=.41), diastolic BP (+0.04±7.36 mmHg; p=.98), mean BP (+0.64±6.42 mmHg; p=.68) or HR (−0.72±5.86 beats/min; p=.61). Differences were not observed even when daytime or nighttime values were separately considered. Though this was not a comparative study, we did not find differences between the effects of the two formulations (24-h mean BP; p=.699).
Conclusions: These data suggest a neutral effect of estradiol-based COCs on independent risk factors for cardiovascular diseases such as BP or HR.
Implications: BP and HR of normotensive women are not increased by E2-based COCs.

Keywords: Contraception; Blood pressure; Estradiol; Dienogest; Heart rate; Nomegestrol acetate

1. Introduction

Combined oral contraceptives (COCs) are known to increase blood pressure (BP). Studies conducted performing office BP measurements have shown that preparations containing higher (≥ 50 μg) doses of ethinyl-estradiol (EE) may increase BP up to 15 mmHg [1,2]. Increases of about 4–5 mmHg BP have been documented with COCs containing lower EE doses [3–5] and confirmed by the few data performed with ambulatory 24-h BP monitoring [6,7]. Even the administration of EE-based hormonal contraceptive with vaginal ring induces an increase of 24-h BP of about 2 mmHg [8]. The clinical implication of this mild BP elevation induced by COCs in healthy normotensive women is unclear [9,10].

It is believed that the hypertensive effect of a COC depends on hepatic activation of the renin-angiotensin-aldosterone system induced by the estrogenic component, in a dose-dependent way [11]. Mineralocorticoid activation causes sodium retention, plasma volume addition and BP increase.

Indeed, when EE is administered in formulations containing drospirenone, a progestin with anti-mineralocorticoid properties, its effect on sodium retention is counteracted and BP does not increase [12]. The estrogenic component of some newer COC formulations is estradiol (E2), whose power in inducing hepatic proteins' synthesis is much lower than the one exerted by EE [11,13–16]. Studies

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performed with office BP measurement have reported a neutral effect of E2-based formulations on BP [17,18]. The objective of this study is to investigate whether neutrality of E2-based oral contraceptives on BP is maintained in the 24-h period.

Heart rate (HR) acceleration is an independent risk factor for cardiovascular diseases [19,20], and it was recently reported with the use of EE-based contraceptives [8,12]. In this study, as a secondary objective, modifications of 24-h HR were evaluated during the use of E2-based COCs.

2. Methods

Between January 2011 and September 2013, a prospective cohort single center study was performed at Modena University Hospital Service for Contraception (Italy). After being informed of the different hormonal and non-hormonal contraceptive options, consecutive eligible women who had spontaneously chosen one of the COCs under investigation were invited by a physician to participate to the study, after having signed a specific informed consent approved by the internal review board of our institution (December 2007) for the use of sensitive data. The study was designed and conducted in full accordance with the World Medical Association Declaration of Helsinki. Each patient paid for her own medicine as in real-life condition.

Medications under study were the available oral combined contraceptives with E2:

(1) Quadriphasic E2 valerate (E2V) plus dienogest (DNG) (Days 1–2, 3 mg E2V; Days 3–7, 2 mg E2V +2 mg DNG; Days 8–24, 2 mg E2V+3 mg DNG; Days 25–26, 1 mg E2V; Days 27–28, placebo) (Klaira®, Bayer Schering Pharma, Milan, Italy).
(2) Monophasic E2 plus nomegestrol acetate (NOMAc) (Days 1–24, 1.5 mg E2+2.5 mg NOMAc; Days 25–28, placebo) (Zoely®, Teva Italia, Milan, Italy).

A detailed medical history and a clinical examination were undertaken at the screening visit. Weight was assessed with the subject wearing light clothes. Height was measured with the subject standing with feet together barefoot. Body mass index (BMI) was calculated as the weight in kilogram divided by the height in squared meters. Glucose and lipid measurements were performed in each subject, as part of routine care, prior to prescribing a hormonal contraceptive.

Inclusion criteria included normotensive healthy women with at the screening visit, BMI<25 kg/m^2, 18–40 years of age (if smoker, <35 years), regular menstrual cycles (cycle length between 26 and 31 days) [21] and a normal cervical smear test in the previous 6 months. Exclusion criteria were pregnancy and/or lactation in the previous 6 months, history of vascular diseases, coagulation and liver disorders or altered thyroid function, the use of hormonal contraception or medicines that could possibly influence BP in the previous 3 months, hypersensitivity to any of the study drug ingredients, alterations in the lipid profile (low-density lipoprotein cholesterol>130 mg/dL or triglycerides values>150 mg/dL) or with glucose intolerance (fasting glucose>110 mg/dL).

Normal BP was diagnosed by office BP measurement using a mercury sphygmomanometer according to the recommendation of the European Society of Cardiology (values equal or lower than 140/90 mmHg in the average of three measurements taken with the subject sitting quietly for 5 min) [22]. Enrollment ended when the number of subjects reached 24. Subjects were enrolled consecutively, and because E2V/DNG was earlier introduced in the market and more popular, more women chose this type of formulation rather than E2/NOMAc.

The final study group consisted of 16 women on E2V/DNG and 8 women on E2/NOMAc.

2.1. Blood samples

All blood samples were collected in the morning, after 12 h of fasting, and analyzed in the same laboratory. Glucose was determined by enzymatic method (instrument Cobas c 501, Roche, Germany). In our laboratory, intra- and inter-assay CV % for glucose were 1.9% and 3.4%, respectively. Plasma total cholesterol and triglycerides were measured by enzymatic colorimetric methods (instrument Cobas c 501, Roche, Germany). High-density lipoprotein (HDL) cholesterol was determined after precipitation with PEG 6000. In our laboratory, intra- and inter-assay CV% for total cholesterol were 2.3% and 2.3%; for triglycerides, 2.5% and 4.1%; and for HDL cholesterol, 4.9% and 3.0%, respectively.

2.2. BP measurement

An oscillometric BP monitoring device (ABP Monitor 90207, Spacelabs Medical, Redmond, WA, USA) was used to measure BP and HR every 30 min consecutively from 5:00 p.m. to 9:00 a.m. of the following second day [23]. The device is used worldwide and it is one of the most accurate devices for BP monitoring. In validation studies in general population, a difference greater than 5 mmHg between the test device and the reference standard was found in less than 30% of the readings [24]. Calibration of the system was checked for each single recording by a full-sized mercury sphygmomanometer, with monitor reading maintained within 3 mmHg of the manometer readings. When unsuccessful at the first try, BP was measured again. Unsuccessful readings were recorded as event codes (subjects movements, heart arrhythmias, unreasonable BP, etc.). Reports were considered appropriate when successful readings exceeded 90% of those expected (>43 correct readings of a total of 48). During the 41-h BP monitoring period, subjects were requested to maintain the arm still and parallel to the trunk when the cuff was inflated. During the daytime, subjects were requested to eat at scheduled times and were allowed to walk but not to engage in vigorous