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Positive effects on cardiovascular and breast metabolic markers of oral estradiol and dydrogesterone in comparison with transdermal estradiol and norethisterone acetate

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Abstract

Objectives: To assess differences in two sequential combined hormone replacement therapy (HRT) products on selected cardiovascular and breast metabolic markers. The products were different concerning the route of administration of estradiol and its combined progestin, either oral or transdermal, and the androgenic properties of progestogens, respectively, dydrogesterone and norethisterone acetate. *Methods:* One hundred and nineteen healthy non-hysterectomized postmenopausal women were included in this open, multi-center, two parallel group trial. They were randomized to a treatment of six 28-day cycles with oral estradiol sequentially combined with dydrogesterone (oE2/D10) or a sequential combination patch of estradiol plus norethisterone acetate (tdE/NETA). At baseline and after six cycles the high-density lipoprotein cholesterol (HDL-C), the sex hormone binding globulin (SHBG) and the total insulin-like growth factor-I (IGF-I) blood levels were determined by a central laboratory. A total of 89 women were compliant to the protocol. *Results:* After six cycles, a statistically significant difference ($P < 0.001$) concerning HDL-C, SHBG and IGF-I levels was found between the two treatment groups. The HDL-C levels were increased in the oE2/D10 group and decreased in the tdE/NETA group, with a final difference of about 0.3 mmol/l. The oE2/D10 treatment induced a sharp increase (about 57 mmol/l) in SHBG levels. IGF-I levels decreased with both the products, but the difference in favor of the oE2/D10 treatment was of about 30 ng/ml. Moreover, patients on tdE/NETA with

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an IGF-I baseline value below the median showed an increase. *Conclusion:* Oral estradiol sequentially combined with dydrogesterone, a non-androgenic progestogen, induced positive changes of some cardiovascular (HDL-C) and breast (SHBG and IGF-I) metabolic markers. These effects were significantly different from those obtained with a transdermal estradiol associated to an androgenic progestogen.

Keywords: Hormone replacement therapy (HRT); High-density lipoprotein cholesterol (HDL-C); Sex hormone binding globulin (SHBG); Insulin-like growth factor-I (IGF-I); Dydrogesterone; Norethisterone acetate (NETA); Mode of administration

1. Introduction

Menopause is becoming an important social issue, considering that most women in developed countries will spend a third of their lives postmenopausally [1].

Hormone replacement therapy (HRT) is highly effective for menopausal symptoms and for prevention of osteoporosis [1].

Epidemiological studies consistently found that women using HRT are at substantially lower risk for coronary heart disease (CHD) [2,3], even if recently published data raised concern about the use of HRT in the secondary prevention of CHD [4]. On the other hand, estrogens showed positive effects on various risk factors for CHD.

Recent observations pointed out to the differences between the routes of administration of estrogens and the androgenic properties of progestogens. The HRT preparations used might account for the conflicting epidemiological results. Estrogens can be given orally or transdermally, the principal difference consisting of the first pass liver metabolism.

The most evident effect of the first pass liver metabolism of oral estrogens is the increase of HDL-cholesterol (HDL-C), which is positively associated with the reduction of the cardiovascular risk.

On the contrary, 19-nortestosterone derived progestogens antagonize the positive effects of orally administered estrogens on HDL-C [5].

Moreover, some metabolic markers such as a decrease in the sex hormone binding globulin (SHBG) and an increase in the insulin-like growth factor-I (IGF-I), which potentially increase breast cancer risk [6], can be reversed by orally administered estrogens. Oral estrogens could lead to an increase in SHBG levels and a decrease in the IGF-I. Both these effects are opposed by progestogens with androgenic properties [7].

Not many studies are published to compare the different HRT preparations. This study was designed to compare two sequential combined HRT products, which were different, concerning the route of administration of estradiol/progestin (respectively, oral or transdermal) and the androgenic properties of progestogens (respectively, dydrogesterone or norethisterone acetate). Dydrogesterone is an orally-active progestogen which is chemically and biologically very similar to the endogenous human progesterone. Norethisterone acetate differs from dydrogesterone in that it is a derivative of 19-nortestosterone and has notable androgenic potency. The primary endpoints were selected to represent two different metabolic systems that were thought to be affected by different administration route of estrogens and/or different androgenic properties of progestogens and to influence cardiovascular or breast cancer risk in women: lipid and SHBG/IGF-I blood levels. It was recognized at the outset that the size and the duration of the trial would not provide adequate power to determine whether any of these hormone regimens influenced cardiovascular disease or breast cancer risk.

The primary endpoints were the HDL-C, the SHBG and total IGF-I blood levels.

2. Materials and methods

This study was an open multi-center, randomized, comparative, two parallel group trial conducted in six gynecological centers in Italy. The open label design was based on the fact that two different pharmaceutical forms were to be tested (oral tablets or patches).