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Folate status and homocysteine levels during a 24-week oral administration of a folate-containing oral contraceptive: a randomized, double-blind, active-controlled, parallel-group, US-based multicenter study☆

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Abstract

Background: This study investigated the effects of adding levomefolate calcium 0.451 mg (the calcium salt of L-5-methyltetrahydrofolate; Metafolin®) to an oral contraceptive containing ethinylestradiol (EE) 20 mcg/drospirenone (drsp) 3 mg on folate levels in healthy women seeking contraception.

Study Design: In this randomized, double-blind, multicenter US-based study, women (18–40 years) received 24 weeks (six cycles) of EE/drsp/levomefolate calcium or EE/drsp for 24 days followed by 4 days of levomefolate calcium alone or placebo, respectively. The primary efficacy variables were red blood cell (RBC) and plasma folate levels at 24 weeks.

Results: At week 24, increases from baseline in mean RBC (990 ± 390 nmol/L to 1406 ± 440 nmol/L) and plasma folate (45.0 ± 17.6 nmol/L to 60.8 ± 19.9 nmol/L) levels were observed in women who received EE/drsp/levomefolate calcium [per protocol set (n=262); all values are displayed as mean ± standard deviation]. In contrast, marginal fluctuations were observed with EE/drsp ($p<.0001$ for between-treatment differences at week 24).

Conclusion: Clinically significant increases in folate status were observed with EE/drsp/levomefolate calcium compared with EE/drsp alone in US women of childbearing age.

Keywords: Drospirenone; Ethinylestradiol; Folates; Oral contraceptives; Neural tube defects

1. Introduction

Neural tube defects (NTDs) are a complex, heterogenous group of congenital nervous system malformations resulting from incorrect or incomplete closure of the neural tube during the early stages of embryonic development [1,2]. Neural tube defects are a leading cause of morbidity and mortality in neonates, with the most common types, anencephaly and spina bifida, occurring in at least 300,000 newborns worldwide each year [3].

The causative mechanisms of NTDs are not yet fully understood, but are believed to be influenced by both genetic and environmental factors [3]. One environmental factor, which is considered to play a key role, is the maternal folate status during the periconceptional period [4–6]. A study by Daly et al. [6] in 1995 showed a quantitative relationship between maternal red blood cell (RBC) folate status and NTD risk; higher RBC folate concentrations were found to be associated with a lower risk of NTDs. Furthermore, substantial evidence has shown that folic acid intake during

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the periconceptional period is associated with a decreased risk of NTDs [7–10].

Consequently, there have been a number of government-led enterprises to increase folate levels in women of childbearing potential, including health education campaigns, folate supplementation policies and food fortification programs. However, despite a general decline in NTD rates over the past 15 years [11,12], NTDs remain a relatively common birth defect in the USA [12,13].

Currently, folic acid supplementation guidelines issued by the US Preventative Services Task Force recommend that all women of childbearing potential take a daily supplement containing 0.400–0.800 mg of folic acid and that supplementation be commenced at least 1 month before conception and continued during the first 2–3 months of pregnancy [14]. However, data indicate that a considerable number of women in the USA do not take regular folic acid supplementation, even those women who are actively planning a pregnancy [15–17].

It has been proposed that oral contraceptives (OCs), the primary method of birth control in many countries, would be an ideal vehicle for folate supplementation in women of reproductive age [18]. This could ensure improved folate levels during the critical early stages of embryonic development in those women who become pregnant soon after stopping OCs or who become pregnant while taking them (primarily due to missing ≥1 tablets [19]). In one study, 21.1% of past OC users analyzed were pregnant one cycle after stopping OC use; after three cycles, the rate of pregnancy had increased to 45.7% [20]. Therefore, women frequently lack adequate counseling about the need for folic acid supplementation before pregnancy. Moreover, many women find it difficult to remember to take a multivitamin on a regular basis [21], whereas data indicate that compliance with OCs is generally high [22]. Thus, combining OCs with folates would also ensure that women receive a regular intake of folate.

L-5-methyltetrahydrofolate (L-5-methyl-THF) is the most prevalent form of dietary folate. Levomefolate calcium (Metafolin®), the calcium salt of L-5-methyl-THF, offers an alternative to folic acid for the improvement of folate status. Ethinylestradiol (EE) 20 mcg/drospirenone (drsp) 3 mg plus levomefolate calcium 0.451 mg (equivalent to L-5-methyl-THF 0.416 mg or an equimolar dose of folic acid 0.400 mg) is a combined OC plus folate supplement, which has been approved in the USA to provide folate supplementation in women of childbearing age who elect to use an OC for birth control. Each cycle provides 24 days of EE 20 mcg/drsp 3 mg/levomefolate calcium 0.451 mg followed by a 4-day hormone-free period with tablets containing levomefolate calcium 0.451 mg only.

Clinical studies have indicated that EE 20 mcg/drsp 3 mg/levomefolate calcium 0.451 mg and EE 30 mcg/drsp 3 mg/levomefolate calcium 0.451 mg increase folate levels in populations that do not participate in a program of mandatory fortification of food and cereal products with folic acid [23–26]. However, it is also of interest to identify whether additional daily intake of folate would yield any further increase in folate status in a population with an established food fortification program.

Clinical trial data indicate that homocysteine is an important marker of pregnancy complications and adverse pregnancy outcomes, and elevated homocysteine levels have been shown to be associated with an increased risk of neonatal complications such as low birth weight and NTDs [27].

Therefore, this study was conducted to investigate the change from baseline in RBC and plasma folate levels, and homocysteine levels during a 24-week oral administration of EE 20 mcg/drsp 3 mg/levomefolate calcium 0.451 mg compared with an established OC containing EE 20 mcg/drsp 3 mg in a US-based population of healthy women seeking contraception.

2. Materials and methods

2.1. Study design

This was a randomized, double-blind, active-controlled, parallel-group study conducted at eight centers in the USA. The study was conducted in accordance with the International Conference on Harmonization/Good Clinical Practice and the principles stipulated by the Declaration of Helsinki. Approval of the Institutional Review Board was acquired for all centers, and written, informed consent was obtained from all women prior to study entry. This trial is registered with ClinicalTrials.gov (NCT00468481).

2.2. Study participants

Healthy female volunteers aged 18–40 years (inclusive) requesting contraception were eligible for inclusion in this study. Women were required to have a normal or nonsuspicious cervical smear at screening or within 6 months prior to screening. The study population was designed to be representative of the US population; women in rural and urban settings were included, as were women of different ethnicities.

Exclusion criteria included smokers aged >30 years; pregnancy or lactation; recent (≤3 menstrual cycles) pregnancy, lactation or abortion; body mass index (BMI) >35; hypersensitivity to any of the study drug ingredients; any disease or condition that could compromise the function of body systems or affect the pharmacokinetics of the study medication; current or history of clinically significant depression, alcohol or drug abuse; treatment with prohibited concomitant medications (including steroid hormones, anticoagulants, antiepileptics, hypnotics or sedatives); less than six menstrual cycles since intramuscular depot contraception at screening visit; less than one menstrual cycle since removal of hormone containing implants at