New Drug

Estradiol Valerate/Dienogest: A Novel Combined Oral Contraceptive

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ABSTRACT

Background: Estradiol valerate/dienogest (E2V/DNG) is a combined oral contraceptive (COC) with 2 new hormonal entities and a unique 4-phasic dosing regimen indicated for women to prevent pregnancy.

Objective: The purpose of this article is to review the pharmacology, pharmacokinetics, clinical efficacy, tolerability, and cost of E2V/DNG.

Methods: MEDLINE (1966–June 2011) and EMBASE (1966–June 2011) were searched for original research and review articles published in the English language using the terms *Natazia* or *Qlaira* or *estradiol valerate and dienogest*. The reference lists of identified articles were reviewed for additional pertinent publications. Abstracts from the 2005 to 2011 American Society of Reproductive Medicine and American College of Obstetricians and Gynecologists meetings were searched using the same terms.

Results: The search provided 56 articles that addressed the pharmacology, pharmacokinetics, pharmacodynamics, clinical efficacy, and tolerability of E2V/DNG in women of reproductive age. Articles reporting efficacy or tolerability in the setting of menopause were excluded. The initial efficacy of E2V/DNG on ovulation inhibition was investigated in 2 prospective, randomized, open-label, Phase II dose-finding studies. The dose that was approved by the Food and Drug Administration resulted in 3.13% of women ovulating in the second cycle of treatment (90% CI, 0.2%–6.05%). Rate of pregnancy prevention with this agent was reported with a Pearl Index ranging from 0.73 to 1.27 (unadjusted) to 0.34 to 0.72 (adjusted for method failure only). The mean duration of withdrawal bleeding was 4.3 days (range, 4.0–4.6 days) among 2266 women receiving 13 treatment cycles. Adverse events reported in >1% of patients included abdominal pain, acne, breast pain, dysmenorrhea, emotional lability, headache, nausea, and weight increase.

Conclusions: Estradiol valerate/dienogest is a new contraceptive formulation. It offers efficacy, tolerability, and an acceptable safety profile with a potentially better bleeding pattern than levonorgestrel-containing COCs. This COC may be especially useful for older women of reproductive age who are adherent to therapy and looking for shorter and/or lighter menstrual cycles. Studies will need to be performed to determine whether clinically significant differences in outcomes exist among E2V/DNG and other available COCs. (*Clin Ther*. 2012;34:37–55)

Key words: contraception, combined oral contraceptives, dienogest, estradiol valerate, oral contraceptives.

INTRODUCTION

Combined oral contraceptives (COCs) contain both an estrogen and progestin component. Significant developments and changes in COCs have occurred since their introduction in the 1960s. The first combined contraceptive pill marketed in the United States in 1961 contained 5 mg of norethynodrel and 75μg of mestranol.*[1] Although a higher dose of this agent containing 9.85 mg of norethynodrel and 150μg of mestranol had been approved in 1960, it was never marketed as a contraceptive.[2] These high doses of hormones were used because they were found to be effective and, at that time, studies

Accepted for publication November 2, 2011.
doi:10.1016/j.clinthera.2011.11.006
0149-2918/$ - see front matter

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were not performed to identify the lowest effective dose. Since those first pills, the doses of sex steroids in COCs have decreased significantly, which has allowed for increased safety and decreased adverse effects.

Research efforts since the 1960s have focused on the effect of estrogen and progestin for effective and safe contraception. Three estrogenic compounds are used in the oral contraceptives (OCs) available in the United States. Mestranol is a prodrug that must be metabolized by the liver into ethinyl estradiol (EE) to have biologic activity. This component was used frequently in the early COCs but is now found only in a few COCs at a 50-μg dose. This mestranol dose is equivalent to approximately 35 to 40 μg of EE.[3] Most COCs available today contain EE as the estrogen component. Ethinyl estradiol has been synthesized since 1938 because the natural estradiol is poorly absorbed when taken orally and is rapidly inactivated by the liver.[1] The substitution at C17 with an ethinyl group on the estradiol component is much more resistant to degradation.[4] This creates a much more potent and longer-acting compound. It allows for once-daily dosing but also has a greater effect on metabolic parameters compared with estradiol.[4] Doses of EE in COCs in the United States vary from 20 to 50 μg daily. Recently, a new estrogen component, estradiol valerate (E2V), has been introduced into a COC in the United States. It is immediately cleaved to estradiol so the circulating molecule reaching the estrogen receptors is the natural 17β-estradiol.[5] Although estradiol is effective in helping to prevent pregnancy, the 17β-estradiol in its natural form causes poor cycle control.[6] When E2V is combined with dienogest (DNG) in multiphasic regimens, it solves the problem of poor cycle control observed with previous 17β-estradiol COCs.[6,7]

The progestin component provides most of the contraceptive activity of the COC. Nine different progestins have been used in the COCs sold in the United States, each with a different potency and different metabolic effects. The progestins are typically categorized into "generations" based on when they were introduced into the United States. The first-generation progestins are norethindrone, norethindrone acetate, and ethynodiol diacetate. Because the dose of these agents was reduced over time, some women began experiencing more unscheduled bleeding and spotting; second-generation progestins were developed in response to these unwanted effects.[3] The second-generation progestins are norgestrel and levonorgestrel (LNG). These compounds are more potent and have longer half-lives than the first-generation progestins.[3] Pills containing these progestins have more androgenic activity, which may be helpful for libido but detrimental for women with hirsutism, acne, or dyslipidemia.[3] Third-generation progestins, desogestrel and norgestimate, were designed to maintain increased progestational activity but reduce androgenic activity. With less androgenic activity, the estrogen component can more fully express itself metabolically.[3] This may be effective for acne, but the increased expression of estrogen may lead to a higher risk of thromboembolic events, especially in COCs containing EE.[3,8] The fourth-generation progestins, drospirenone and DNG, have been designed to specifically bind to the progesterone receptor without any interaction with other steroid receptors.[8]

Several innovations have been introduced over the years in COC formulations and packaging. Formulations may vary by the type and amount of hormones, the patterns of those amounts throughout the cycle, and the number of active pills in the packet. Monophasic formulations have active pills that contain the same amount of estrogen and progestin. Multiphasic formulations have estrogen and progestin amounts that vary. Biphasic formulations have 2 different combinations of estrogen and progestin, and triphasic formulations have 3 different combinations. Recently, a 4-phasic formulation has been introduced with an estrogen step-down and progestin step-up sequence.[9]

Most COC packages contain 21 active (containing hormone) pills with 7 placebo (inert) pills; these packages are known as 21/7 regimens. During the placebo week, a withdrawal bleed occurs. Early in COC development, this was valid because at that time rapid pregnancy tests were not available and it reassured women they were not pregnant. As doses of estrogen and progestin have decreased in COCs, serum levels decrease low enough for endometrial sloughing to begin within 2 to 3 days of the last active pill.[3] Decreasing the number of placebo pills in low-dose formulations is necessary to prevent recruitment of follicles.[10,11] Therefore, several formulations with shortened hormone-free intervals are now available in 24/4 or 26/2 regimens.

As COCs have evolved, it has become clear that individual women have individual needs for contraception. Approximately 38 million women (98% of 43 million fertile, sexually active women) in the United States are practicing contraception.[12] Twenty-eight percent of them are choosing a COC as their primary method.[12] The pill is