Maturitas 74 (2013) 375–382

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Bioidentical compounded hormones: A pharmacokinetic evaluation in a randomized clinical trial☆

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ARTICLE INFO

Article history:
Received 10 December 2012
Received in revised form 11 January 2013
Accepted 12 January 2013

Keywords:
Bioidentical
Compounded
Hormone therapy
Pharmacokinetics

ABSTRACT

Objective: Bioidentical compounded hormone therapy is popular among patients, but providers do not have pharmacokinetic information or dosing guidelines for these preparations. Our objective was to compare the pharmacokinetics of the commonly used compounded preparations with conventional hormonal preparations that are considered bioequivalent in practice.
Methods: We conducted a randomized, blinded, four-arm 16-day clinical trial of forty postmenopausal women assigned to one of three doses of a compounded estrogen cream (Bi-est (80:20); 2.0, 2.5, or 3.0 mg) + compounded oral progesterone 100 mg, or to a conventional estradiol patch (Vivelle-Dot™ 0.05 mg) + Prometrium™ 100 mg. Serum levels of estrone, estradiol, estriol, and progesterone were obtained at multiple time intervals during the first 24-h, and at steady-state.
Results: Results were analyzable for 37/40 women. Study medications were well tolerated. The AUC at 24 h and at steady-state for estrogens remained consistently lower for all doses of Bi-est tested relative to the patch. The difference was statistically significant for Bi-est 2.0 mg (AUC-estradiol = 181 vs. 956; $p < 0.001$) and 2.5 mg (AUC-estradiol = 286 vs. 917; $p < 0.001$). Estriol levels remained low in all study arms. Serum progesterone levels were comparable in conventional vs. compounded groups.
Conclusions: This pharmacokinetic trial showed that the currently used doses of compounded hormones yield lower levels of estrogen compared to the standard-dose estradiol patch. To find comparable doses, further studies are needed. This successfully conducted randomized controlled study attests to the feasibility of using a similar design in the setting of a larger clinical trial.

1. Introduction

With an aging population globally, the world's total menopausal population, estimated at 476 million in 1990, is expected to rise to 1.2 billion by 2030 [1]. In the United States, approximately 75%–80% of postmenopausal women report vasomotor symptoms [2]. A large proportion of these women also experience vaginal dryness [3], urinary incontinence [3], decline in sexual interest and satisfaction [4], mood fluctuations [5,6], sleep disturbances [7–9], and changes in memory and cognition, for which hormone therapy is often sought. The collective impact of these symptoms on women's well-being is enormous, and the need for safe treatments is compelling [10].

Conventional hormone therapy consisting of Food and Drug Administration (FDA)-approved products is the standard of care in the United States when treatment is indicated for menopausal symptom relief. However, randomized trials such as the Heart and Estrogen/Progestin Replacement Study [11] and Women's Health Initiative [12] raised concerns about the safety of conventional hormones like Premarin™ and Provera™, leading to a marked reduction in their use and creating a demand for safer alternatives.

Bioidentical hormones have gained popularity as possible alternatives to conventional hormones. The term "bioidentical"

Abbreviations: CRU, Clinical Research Unit; CVs, coefficient of variations.
☆ *Trial registration*: linicaltrials.gov identifier: NCT00864214.
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http://dx.doi.org/10.1016/j.maturitas.2013.01.010

Table 1
Study design.

No. of patients/arm	Randomization				
	Active intervention		Placebo	Intervention phase (16 days)	
	Estrogen	Progesterone		Day 1	Days 15 and 16
10	Bi-est 2.0 mg	Compounded progesterone 100 mg	Patch	Serial measurements E1, E2, E3	Serial measurements E1, E2, E3;
10	Bi-est 2.5 mg	Compounded progesterone 100 mg	Patch	Baseline and 24 h progesterone level	Single end-of-treatment progesterone level
10	Bi-est 3.0 mg	Compounded progesterone 100 mg	Patch	Monitoring for adverse effects	Monitoring for adverse effects
10	Estradiol 0.05 mg patch (Vivelle-Dot™)	Micronized progesterone 100 mg capsule (Prometrium™)	Cream		

implies a chemical and molecular structure precisely the same as its endogenous human hormone counterpart. Structural similarity by some is believed to correlate with safety, a perception that has led to a sharp increase in the popularity of bioidentical hormones.

Currently there are multiple FDA-approved conventional hormone products that are plant-derived and bioidentical in chemical structure [13]. However, likely due to extensive media coverage, requests from women for bioidentical hormones are predominantly for the *compounded* preparations. In the absence of adequate research, no clear guidelines exist for choosing the most appropriate type, dose, or regimen of bioidentical compounded hormones. Lacking this data, it is challenging to study these preparations for safety and efficacy.

To the best of our knowledge, no pharmacokinetic studies have compared conventional with compounded bioidentical hormones. Compounding pharmacists generally consider Bi-est (referring to estriol plus estradiol) in a dose of 2.5 mg (for example, in a ratio of 80% estriol plus 20% estradiol, which consists of 2 mg estriol and 0.5 mg estradiol) as approximately equivalent to a mid-range dose of an estradiol-containing patch such as Vivelle-Dot™ 0.05 mg. Thus, using Bi-est with 80% estriol and 20% estradiol, and comparing the calculated estradiol equivalence of the compounded preparations with the daily referenced estradiol dose of the patch, we assigned the three strengths of creams to create a reasonable range for comparison.

In order to lay the groundwork for future trials, we conducted a pharmacokinetic study as a randomized, blinded clinical trial. Our intent was to compare estrogen and progesterone levels obtained following the administration of bioidentical compounded hormone therapy preparations both with themselves and with conventional hormone therapy.

2. Methods

2.1. Subjects

The study was approved by the Mayo Clinic Institutional Review Board. Since estriol is not an approved product in the United States, an IND (investigational new drug) application was filed with the US-FDA. This was a Phase I, blinded, randomized, four-arm study. Subjects were recruited from Rochester, MN, and surrounding areas through advertisements and news media releases. Eligibility was based on the following criteria:women 40–60 years old, naturally postmenopausal (absence of periods for ≥1 year or amenorrhea for ≥6 months and FSH ≥40 IU/L) or surgically postmenopausal (menopause induced by removal of ovaries), able to understand and sign an informed consent, and willing to stay overnight in a Clinical Research Unit (CRU). Eligible women had normal results on screening tests (AST, creatinine, and TSH within 20% of the upper limit of normal) and a negative mammogram within the last 11 months. Presence or absence of menopausal symptoms was not used as an eligibility criterion. Subjects were excluded using the following criteria: estrogen levels >35 pg/mL; >10 years from last menstrual period; a history of cancer of the breast, uterus or ovary, coronary artery disease, stroke, dementia, migraine, deep venous thromboembolism, active liver or gall bladder disease, uncontrolled hypertension, diabetes, or lupus; currently smoking; alcohol or substance abuse; family history of premenopausal breast or ovarian cancer; or postmenopausal breast cancer in ≥2 relatives. Recent use of hormone therapy was allowed with an adequate washout period (at least 1 week for vaginal hormones, 4 weeks for transdermal hormones, and 8 weeks for oral hormones). Additional exclusions included peanut allergy, current use of isoflavone-containing products, and drugs or herbs that might affect metabolizing enzymes.

2.2. Study treatment

Eligible women were randomized to one of four treatment arms in a double-blinded fashion. Three study arms included compounded estradiol–estriol cream (Bi-est) in varying dosage, along with a placebo skin patch, and compounded oral micronized progesterone capsules. The fourth arm included an estradiol-containing patch (Vivelle-Dot™), placebo cream, and commercially available oral micronized progesterone capsules (Prometrium) (Table 1).

Bi-est (80:20) 2.5 mg was chosen as it is considered equivalent to 0.05 mg estradiol patches in compounding practice. Bi-est was compounded in Vanicream and dispensed in premarked individual syringes by an experienced compounding pharmacist (RAW), who was blinded to the participants' study group assignment. Women in study arm one received Bi-est 2.0 mg (1.6 mg estriol and 0.4 mg estradiol), in arm two Bi-est 2.5 mg (2 mg estriol and 0.5 mg estradiol), and arm three Bi-est 3.0 mg (2.4 mg estriol and 0.6 mg estradiol). Women in study arm four received Vivelle-Dot 0.05 mg patches.

On day one of the study, participants were admitted to the hospital in the CRU, where they were instructed to apply their first dose under supervision by trained nurses. The creams were applied to a specified area of the forearm by gentle rubbing for 1 min. The Vivelle-Dot™ patch was applied to the skin of the lower abdomen following the manufacturer's directions. The capsules were administered orally under supervision. Throughout the next 24 h, serial blood samples were obtained at specified intervals to measure the serum levels of estrogen fractions and progesterone (Table 2). After 24 h of the CRU stay, participants were discharged and continued taking study medications as instructed. They returned on the 15th day of the study and were admitted for 12 h during which time serial blood samples were obtained to measure the steady-state