ELSEVIER

Contraception 90 (2014) 550 – 556

Contraception

Original research article

Correcting oral contraceptive pharmacokinetic alterations due to obesity: a randomized controlled trial☆,☆☆,★

Alison B. Edelman[a,*], Ganesh Cherala[a,b], Myrna Y. Munar[b], Martha McInnis[a], Frank Z. Stanczyk[c], Jeffrey T. Jensen[a]

[a]*Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, OR 97239, USA*
[b]*Oregon State University and Oregon Health & Science University College of Pharmacy, Portland, OR 97239, USA*
[c]*Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA*

Received 19 October 2013; revised 18 June 2014; accepted 19 June 2014

Abstract

Objective: To determine if increasing the hormone dose or eliminating the hormone-free interval improves key pharmacokinetic (PK) alterations caused by obesity during oral contraceptive (OC) use.
Study design: Obese [body mass index (BMI)≥30 kg/m^2], ovulatory, otherwise healthy, women received an OC containing 20 mcg ethinyl estradiol (EE)/100 mcg levonorgestrel (LNG) dosed cyclically (21 days active pills with 7-day placebo week) for two cycles and then were randomized for two additional cycles to the following: continuous cycling (CC, a dose neutral arm using the same OC with no hormone-free interval) or increased dose (ID, a dose escalation arm using an OC containing 30 mcg EE/150 mcg LNG cyclically). During Cycles 2, 3 and 4, outpatient visits were performed to assess maximum serum concentration (C_{max}), area under the curve ($AUC_{0-\infty}$) and time to steady state as well as pharmacodynamics. These key PK parameters were calculated and compared within groups between baseline and treatment cycles.
Results: A total of 31 women enrolled and completed the study (CC group, n=16; ID group, n=15). Demographics were similar between groups [mean BMI: CC, 38 kg/m^2 (S.D. 5.1); ID, 41 kg/m^2 (S.D. 7.6)]. At baseline, the key LNG PK parameters were no different between groups; average time to reach steady state was 12 days in both groups; C_{max} were CC: 3.82±1.28 ng/mL and ID: 3.13±0.87 ng/mL; and $AUC_{0-\infty}$ were CC: 267±115 h ng/mL and ID: 199±75 h ng/mL. Following randomization, the CC group maintained steady-state serum levels whereas the ID group had a significantly higher C_{max} ($p<.001$) but again required 12 days to achieve steady state. However, AUC was not significantly different between CC (412±255 h ng/mL) and ID (283±130 h ng/mL). Forty-five percent (14/31) of the study population had evidence of an active follicle-like structure prior to randomization and afterwards this decreased to 9% (3/31).
Conclusion: Both increasing the OC dose and continuous dosing appear to counteract the impact of obesity on key OC PK parameters.
Implications: Obesity adversely affects the pharmacokinetics of very low dose OC pills. Although the impact of these changes on OC efficacy is still under debate, PK parameters can be normalized in obese users by continuous dosing or increasing to a low-dose pill.
© 2014 Elsevier Inc. All rights reserved.

Keywords: BMI; Drug levels; Hormonal contraception; Continuous dosing

☆ Clinical trials number: NCT01170390.

☆☆ Authors Disclosures: Dr. Edelman: consultant for Gynuity Health Projects, Genzyme and Agile Therapeutics; Nexplanon trainer for Merck; and author for UptoDate (Royalties received). She receives research funding from the National Institute of Health and the Bill & Melinda Gates Foundation. These potential conflicts of interest have been reviewed and managed by Oregon Health & Science University (OHSU). Dr. Jensen has received payments for consulting from Bayer Healthcare, Merck, Agile Therapeutics, HRA Pharma and the Population Council and for giving talks for Bayer and Merck. He has also received research funding from Abbott Pharmaceuticals, Bayer, the Population Council, the National Institute of Health and the Bill & Melinda Gates Foundation. These companies and organizations may have a commercial or financial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU. Dr. Stanczyk is presently on the advisory board for Merck & Co., Inc. and Agile Therapeutics. Also, in the last few years, he has consulted for Shionogi Inc. and Bayer Healthcare. Ms. McInnis and Drs. Munar and Cherala have no disclosures.

★ Financial Support: The authors acknowledge the grant support from the National Institutes of Health (R01 HD061582-01 NICHD; 2K12HD043488 NICHD), the OHSU Oregon Clinical & Translational Research Institute (NIH NCRR 1 UL1 RR024120) and the Bioanalytical Shared Resource/ Pharmacokinetics Core at OHSU.

* Corresponding author. Ob/Gyn Dept, Mail Code UHN 50, Oregon Health & Science University, Portland, OR 97239, USA. Tel.: +1-503-418-2585.
E-mail address: edelmana@ohsu.edu (A.B. Edelman).

http://dx.doi.org/10.1016/j.contraception.2014.06.033
0010-7824/© 2014 Elsevier Inc. All rights reserved.

1. Introduction

Obesity impacts the pharmacokinetic (PK) parameters of contraceptive steroids: specifically, half-life, clearance, area under the curve and time to achieve steady state [1,2]. These PK indices are considered critical indicators of drug therapeutic performance [3]. Whether the observed alterations in PK parameters observed in obese women translate into clinical evidence of failure (i.e., pregnancy) is controversial, but observed PK changes are concerning and may magnify the effects of poor pill compliance in this population [4]. Although it is tempting to simply recommend alternative forms of birth control to bypass both PK and compliance issues, oral contraceptives (OCs) remain the most popular form of contraception [5] and a woman's individual preference influences her compliance and continuation with any method [6]. Moreover, since obese women have been largely excluded from premarketing evaluations of the newest low-dose formulations of OCs, we have insufficient information available to assess efficacy in this population.

Strategies to normalize PK parameters should improve effectiveness whether the mechanism of failure is altered drug metabolism or poor compliance. We have shown that the most likely 'window for failure' for obese OC users is with pill initiation or following the 7-day hormone-free interval due to a delay in achieving steady state because of changes in contraceptive steroid clearance and not volume of distribution [1]. Following a 7-day hormone-free interval, women of normal body mass index (BMI) achieve a steady-state level of levonorgestrel (LNG) within 5 days whereas obese women take twice as long [1]. We hypothesized that two readily available strategies — eliminating the hormone-free interval [continuous cycling (CC)] or using a higher-dose pill cyclically [increased dose (ID)] — might have the potential to counteract this obesity-related change in OC PK. This study was designed to determine if increasing the hormone dose or eliminating the hormone-free interval resolves the impact of obesity on PK and improves end-organ suppression.

2. Materials and methods

A prospective randomized study was conducted at Oregon Health & Science University (OHSU) in Portland, Oregon from January 2010 to June 2011. The OHSU Institutional Review Board and OHSU Clinical & Translational Research Institute approved the study protocol and all subjects underwent informed written consent.

Otherwise healthy, obese (BMI≥30 kg/m^2) reproductive-aged (18–35 years old) women, not currently using hormonal contraception but seeking to initiate combination OCs, were recruited. Inclusion and exclusion criteria included regular menstrual cycles, not actively seeking weight gain or loss, no evidence of anemia (hematocrit≥36%), no contraindications to hormonal contraception, no use of tobacco or drugs known to interfere with the metabolism of sex steroids and no overt clinical features of or prior treatment for metabolic disorders (i.e., polycystic ovarian syndrome, diabetes).

In addition to baseline demographic information, several obesity biomarkers including weight, height and body composition measurements by air displacement plethysmography were collected. A blood sample was obtained to measure progesterone (P) levels during the luteal phase of the pretreatment cycle to confirm ovulation. A value of ≥3 ng/mL was required for enrollment.

All qualifying study subjects were placed on a combination monophasic birth control pill containing 20 mcg ethinyl estradiol (EE)/100 mcg LNG (Aviane; Teva; Israel) at the onset of menses following the pretreatment cycle. The medication was dosed in a cyclic fashion (21 days active pill with a 7-day hormone-free interval) for a total of two treatment cycles [7]. Randomization to study groups occurred after the completion of these two baseline cycles. Women were then randomized to one of two arms for another two cycles: continuous cycle (CC, a dose neutral arm using the same OC with no hormone-free interval) or ID (a dose escalation arm using an OC containing 30 mcg EE/150 mcg LNG cyclically) (Portia; Barr Laboratories; USA). Subjects were randomized to treatment group by the OHSU Research Pharmacy using a predetermined computer-generated randomization scheme and were allocated using sequentially numbered, opaque, sealed envelopes. Once randomized, women and study staff were not blinded to group allocation. The randomization scheme was provided to the primary investigator after enrollment and data entry were completed.

Women were instructed to take each pill at 9:00 a.m. daily. Self-reported compliance with the medication was recorded on a calendar (compliant cycle≤two late and/or missed pills during 1 cycle) and confirmed based on OC serum levels (nonuser, all LNG values<0.16 ng/mL; inconsistent user, two or more values<1.0 ng/mL; consistent user, no more than one value<1.0 ng/mL) [8].

To determine baseline PK parameters of EE and LNG, serial serum samples were collected during a clinical research inpatient stay beginning on Cycle 1, Day 21 [last day of active pills, 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h], and continuing with daily samples on Cycle 1, Days 22, 23, 24 and 27 (e.g., hormone-free interval in Cycle 1). Outpatient serum samples were obtained to compute the time to reach steady state, maximum serum concentration (C_{max}) and area under the curve ($AUC_{0-\infty}$): twice weekly during Cycles 2, 3 and 4 as well as daily samples in Cycle 3 on Days 22, 23 and 24. Additional serum samples were obtained for FSH, LH, estradiol (E_2) and P at these visits. Exact serum sampling time in relationship to pill ingestion was accounted for in the PK analysis. At each of these visits, a vaginal probe ultrasound (GE LOGIQ 400 Proseries ultrasound, 7.5 MHz) was performed to monitor growth of ovarian follicles. The total number of antral follicles (≥4 mm) was documented and the largest follicle on each ovary was measured in two

Download English Version:

https://daneshyari.com/en/article/3913784

Download Persian Version:

https://daneshyari.com/article/3913784

Daneshyari.com