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Contraception xx (2017) xxx – xxx

Contraception

Original research article

Pharmacokinetics of levonorgestrel and ulipristal acetate emergency contraception in women with normal and obese body mass index☆,☆☆

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Received 10 July 2016; revised 10 December 2016; accepted 15 January 2017

Abstract

Objective: This study compares the pharmacokinetics (PK) of levonorgestrel (LNG) emergency contraceptive (EC) and ulipristal acetate (UPA)-EC between normal-body mass index (BMI) and obese-BMI women.

Study design: This prospective, randomized crossover study evaluates the PK of women after single doses of LNG-EC (1.5 mg) and UPA-EC (30 mg). Study procedures took place during clinical research unit admissions, where participants received a standardized meal and each study drug, in random order, during two separate 24-h admissions. Study staff collected 14 blood specimens (0, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 and 48 h). We evaluated serum concentrations of LNG and UPA using liquid chromatography–tandem mass spectroscopy and estimated the PK parameters of both drugs using noncompartmental analysis. The main outcome of this study was a comparison of between-group differences in AUC_{0-24}.

Results: Thirty-two women completed the study (16 in each group). Among normal-BMI and obese-BMI participants, the mean BMIs were 22.0 (range 18.8–24.6) and 34.3 (range 30.6–39.9), respectively. After LNG-EC, mean AUC_{0-24} and maximum concentration (C_{max}) were 50% lower among obese-BMI women than among normal-BMI women (AUC_{0-24} 100.8 vs. 208.5 ng*h/mL, $IQR_{obese\text{-}BMI}$ 35.8, $IQR_{normal\text{-}BMI}$ 74.2, $p \leq .01$; C_{max} 10.8 vs. 18.2 ng/mL, p=.01). After UPA-EC, AUC_{0-24} and C_{max} were similar between obese-BMI and normal-BMI women (AUC_{0-24} 362.5 vs. 293.5 ng*h/mL, $IQR_{obese\text{-}BMI}$ 263.2, $IQR_{normal\text{-}BMI}$ 375.9, p=.15; C_{max} 95.6 vs. 89.3 ng/mL, p=.70).

Conclusion: After a single dose of EC, obese-BMI women are exposed to lower concentrations of LNG and similar concentrations of UPA, when compared to normal-BMI women.

Implications: Differences in LNG-EC PK by BMI group may underlie and account for the lower LNG-EC efficacy reported among obese-BMI women, but modest differences in UPA-EC PK by BMI group provide less support for variable efficacy. A pharmacodynamic study may be able to clarify whether these PK differences account for observed differences in LNG-EC and UPA-EC efficacy.

Keywords: Emergency contraception; Levonorgestrel; Ulipristal acetate; Obesity; Pharmacokinetics

☆ Funding/Support: The Society of Family Planning funded this project, and had no involvement in the design, conduct, analysis, or interpretation of results. The project also received support from the Irving Institute for Clinical and Translational Research at Columbia University Medical Center and National Center for Advancing Translational Sciences, National Institutes of Health, through Grant No. UL1 TR000040. The content is solely the responsibility of the authors and does not represent the official views of the NIH.

☆☆ Conflicts of interest: C.L.W. is a paid consultant to Agile Therapeutics, Bayer and Merck. Columbia University receives funds for contraceptive research from ContraMed, Estetra SPRL, Leon Farma and Medicines360. A.R.D. is a paid consultant to Bayer. The remaining authors report no financial relationships to any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

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http://dx.doi.org/10.1016/j.contraception.2017.01.004
0010-7824/

1. Introduction

Emergency contraceptive (EC) efficacy trials conducted in the United States and Europe suggest a relationship between obese body mass index (BMI; kg/m^2) and increased EC pill failure, especially levonorgestrel (LNG) EC failure [1,2]. Those analyses showed that the odds of pregnancy after EC were substantially greater [odds ratio (OR) 4.4, 95% confidence interval (CI) 2.05–9.44] for obese-BMI women who took LNG-EC compared to normal-BMI women who took the same dose of LNG-EC. The odds of pregnancy for obese-BMI women who took ulipristal acetate (UPA) EC were also somewhat elevated above that for normal-BMI women (OR 2.6, 95% CI 0.89–7.00). In contrast, a meta-analysis of data from three World Health Organization EC studies showed little difference in LNG-EC efficacy by BMI [3].

The main mechanism of action of EC pills is to inhibit ovulation. Once ingested, LNG-EC and UPA-EC are plasma protein-bound. The majority of the former binds to sex hormone-binding globulin (SHBG) and the majority of the latter to high-density lipoprotein. Obesity is associated with lower concentrations of both proteins, which may result in lower systemic concentrations of LNG and UPA in obese-BMI compared to normal-BMI women. In addition, higher weight has been associated with lower systemic absorption of LNG [4]. Whether potential differences in EC pill efficacy among obese-BMI women results from failure to achieve and/or to maintain systemic drug concentrations that are similar to normal-BMI women is unknown. We carried out this study to describe and compare pharmacokinetic (PK) parameter estimates of normal-BMI and obese-BMI women after exposure to single doses of LNG-EC and UPA-EC.

2. Materials and methods

This prospective, randomized crossover study of LNG and UPA systemic exposure in women receiving single-dose EC pills took place at Columbia University Irving Medical Center, New York, NY, USA, after Institutional Review Board approval. Participants received LNG and UPA-EC pills during separate 24-h admissions from July to December 2015. The trial was registered at ClinicalTrials.gov (NCT 02689804). English-speaking women aged 18–45 years with either normal BMI (18.5–24.9 kg/m^2) or obese BMI (30.0–39.9 kg/m^2) and in good general health were eligible for participation. No participant required EC for therapeutic purposes during this study.

We excluded women who had used a hormonal EC within the past month and did not permit EC or hormonal contraceptive use during the study. Additional exclusion criteria were (1) medroxyprogesterone use within 6 months or LNG-IUS, etonogestrel implant or combined hormonal contraception use within 1 month; (2) menstrual cycles <21 days or >35 days; (3) current breastfeeding or pregnancy within the past 2 months; (4) history of cancer other than non-melanoma skin cancer; or (5) current use of medications known to affect sex steroid metabolism.

Study participation comprised five visits over an 8-week period. After telephone screening, women attended an enrollment visit. During this visit, research staff confirmed eligibility, obtained written informed consent and conducted a brief history and physical exam. Staff measured participants' height and weight in minimal outerwear and used the same stadiometer and scale throughout the study. We generated the order scheme using www.randomizer.org. The US Food and Drug Administration (FDA)-approved study drugs included an EC pill containing 1.5 mg of LNG (Next Choice One Dose™; Actavis Pharma, Parsippany, NJ, USA) and an EC pill containing 30 mg of UPA (ella®; HRA Pharma, Paris, France).

During admission 1, participants completed their first 24-h PK assessment. We instructed participants to fast for 8 h prior to the admission visit, which took place at the Irving Institute for Clinical and Translational Research (IICTR). Upon admission, IICTR research staff placed an indwelling catheter in the participant's upper extremity and collected a baseline venous blood sample (t_0). Next, participants received a 400-cal meal containing 20% fat. To minimize variation in gastric emptying and study drug bioavailability, IICTR Bionutrition Research Core staff collected participants' meal trays and conducted weigh-backs in order to calculate the proportion of calories and fat left unconsumed prior to study drug ingestion. Thirty minutes after completing the standardized meal, participants received the assigned EC pill. Research nurses collected 12 timed venous blood samples ($t_{0.5}$, $t_{1.0}$, $t_{1.5}$, t_2, t_3, t_4, t_6, t_8, t_{10}, t_{12}, t_{16}, t_{24h}). Participants returned at t_{48h} to provide an additional blood sample, and to complete a brief satisfaction survey. We separated each admission by at least 8 days, approximately 8 half-lives of LNG-EC or 5 half-lives of UPA-EC, to allow for washout of the first EC dose. During admission 2, participants completed the same procedures and received the second study drug. We did not restrict either admission to a particular time in the menstrual cycle. Women received financial compensation at the conclusion of each study visit. Maximum total compensation was $775.

Blood samples were allowed to clot at room temperature for 30–60 mins, and then separated by centrifugation (3000 r·min^{-1}, 4 °C, 10 min), and stored in 1 mL aliquots at −80 °C.

2.1. Laboratory methods

Scientists (S.C., R.N.) at the IICTR Biomarkers Core laboratory used ultra-performance liquid chromatography–tandem mass spectroscopy (LC–MS/MS) after liquid–liquid extraction using hexane-dichloromethane to quantify total LNG concentrations. This lab technique uses deuterated LNG (LNG-D7) as internal standard. Intra- and inter-assay precisions are 3% and 6%, respectively. The assay is linear between 0.1 and 100 ng/mL and has a lower limit of quantification of 0.1 ng/mL.

Similarly, these scientists measured UPA in serum by LC–MS/MS after liquid–liquid extraction using deuterated