Contraception 94 (2016) 52 – 57

Contraception

Original research article

Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing☆,☆☆,★

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Received 2 November 2015; revised 2 March 2016; accepted 13 March 2016

Abstract

Objective: To determine if differences exist in the pharmacokinetics (PK) of levonorgestrel-based emergency contraception (LNG-EC) in obese and normal body mass index (BMI) users and test whether doubling the dose of LNG-EC in obese women increases total and free (active) LNG serum concentrations.

Study design: Healthy, reproductive-age women with obese and normal BMIs received 1.5 mg LNG orally (ECx1) and then in a subsequent menstrual cycle, the obese group also received 3 mg LNG (ECx2). Dosing occurred during the follicular phase. Total and free LNG PK parameters were obtained via serum samples through an indwelling catheter at 0, 0.5, 1, 1.5, 2, and 2.5 h. The primary outcome was the difference in total and free LNG concentration maximum (Cmax) between ECx1 and ECx2 in the obese group.

Results: A total of 10 women enrolled and completed the study (normal BMI=5, median 22.8 kg/m^2, range 20.8–23.7; obese BMI=5, 39.5 kg/m^2, range 35.9–46.7). The total LNG Cmax for obese subjects following ECx1 (5.57±2.48 ng/mL) was significantly lower than the level observed in normal BMI women (10.30±2.47, p=.027). Notably, ECx2 increased the Cmax significantly (10.52±2.76, p=.002); approximating the level in normal BMI subjects receiving ECx1. Free LNG Cmax followed a similar pattern.

Conclusion: Obesity adversely impacts both the total and free Cmax levels of LNG EC and this likely explains its lack of efficacy in obese women. Doubling the dose appears to correct the obesity-related PK changes but additional research is needed to determine if this also improves EC effectiveness in obese women.

Implications: This study demonstrates that obesity interferes with the pharmacokinetics of LNG EC, and that doubling the dose may be an effective strategy to improve its efficacy in obese women.

Keywords: pharmacokinetics; obesity; body weight; emergency contraception

☆ Clinical trials#: NCT02408692.

☆☆ AuthorsDisclosures: A. Edelman: consultant forWorld Health Organization, GynuityHealth Projects, Genzyme, andAgile Therapuetics. Nexplanon trainer for Merck. Author for UptoDate (Royalties received). J. Jensen has received payments for consulting from Agile Pharmaceuticals, Abbvie Pharmaceuticals, Bayer Healthcare, ContraMed, Evofem Inc., HRA Pharma, Merck Pharmaceuticals, Microchips, Teva Pharmaceuticals and the Population Council. He has also received research funding from Abbvie, Bayer, Merck, FHI360, Medicines 360, the Population Council, 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. G. Cherala, S Blue, and D Erikson have nothing to disclose.

★ Financial Support: Support for this research was from Medical Research Foundation of Oregon (Grant #1501) as well as grant support from National Institutes of Health the OHSU Oregon Clinical & Translational Research Institute (NIH NCRR 1 UL1 RR024120).

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http://dx.doi.org/10.1016/j.contraception.2016.03.006
0010-7824/

1. Introduction

Approximately 50% of all pregnancies in the United States are unintended [1]. The availability of emergency contraception (EC) provides women with an additional line of defense against unintended pregnancy following unprotected intercourse with the potential to decrease the risk of pregnancy by 81–90% [2]. The leading form of EC, known as Plan B One Step® or Next Choice®, is available over-the-counter in the U.S. to adults and following a recent court decision (2013), is available to adolescents as well. The use of EC among reproductive-age women has doubled from 2006 to 2008 [3] and is likely to continue increasing with this recent legislative change. Unfortunately, the levonorgestrel (LNG)-based method appears to be significantly less effective in obese women, failing 4 times as often as in non-obese women [4]. The mechanism for this phenomenon is unknown but likely due to differences in LNG pharmacokinetics (PK) and not patient adherence given that EC is a single-dose therapy.

As a single-dose therapy, EC is likely reliant on achieving a rapid peak level at a critical time point prior to the LH surge [5–7]. Drug levels were not done in the Glasier [4] study but we suspect that the changes in LNG PK caused by obesity likely resulted in lower peak levels or a delay in time to reach the therapeutic level. Obesity has been proven to adversely affect the PK of combined oral contraceptives containing LNG and ethinyl estradiol, in particular half-life and clearance; these in turn, cause a delay in achieving maximum concentration (Cmax) levels and steady state [8–12]. As the PK profile of the LNG-EC is similar to that of LNG-based OCs, only a magnitude higher due to differences in the dosage [13], we believe these changes could explain the failure seen in EC users. We hypothesize that obesity impacts LNG PK such that the critical peak level needed to prevent the LH surge and ovulation is not achieved. However, baseline differences between normal and obese BMI EC-users have not been studied.

LNG clearance is highly dependent on the availability of unbound drug [14]. LNG is a highly bound drug, mainly to SHBG, with only a small fraction unbound (2–3%) [15,16]. In theory, drug clearance is a function of blood flow to the organ, drug enzyme/transporter activity (i.e. intrinsic clearance) and plasma protein binding. For a low clearance drug like LNG, blood flow is less critical thus plasma protein binding and intrinsic clearance are highly influential. Compared to normal BMI women, levels of sex hormone binding globulin are lower in the obese [17]. Since LNG is bound to SHBG, free fraction of hormone could be elevated resulting in unpredictable effects on clearance. Furthermore, it is unclear whether SHBG associated increase in free fraction would also alter free concentrations, the pharmacologically active form of the drug.

Due to the safety of progestins even at higher doses, many health care providers and expert panels have recommended that obese women take double the LNG EC dose (e.g. "take two") to increase the effectiveness of the method. Although this strategy is one commonly used in pharmacotherapeutics [18], there is currently no evidence to support this approach for obese EC users.

The objectives of this study are to determine if differences exist in the PK of LNG-EC in obese and normal BMI-users, and to test whether dose escalation of LNG-EC in obese women increases total- and free-LNG levels. The overall goal of this research is to improve EC effectiveness and quality of clinical care for obese women seeking EC.

2. Materials and methods

A prospective open-label study was conducted at Oregon Health & Science University (OHSU) in Portland, Oregon from March 2015 to August 2015. The OHSU Institutional Review Board approved the study protocol and all subjects underwent informed written consent.

Otherwise healthy, obese (BMI $\geq$ 30 kg/m^2, n=5) and normal (BMI<25 kg/m^2, n=5) reproductive-aged (18–35 years old) women with regular menstrual cycles (21–35 days) were recruited. Subjects were required to be either heterosexually abstinent or, if heterosexually active, to use a non-hormonal, non-IUD method of contraception. Major exclusion criteria included: metabolic disorders including uncontrolled thyroid dysfunction and Polycystic Ovarian Syndrome; impaired liver or renal function; actively seeking or involved in a weight loss program (must be weight stable); pregnancy, breastfeeding, or seeking pregnancy; recent (8 week) use of hormonal contraception; current use of drugs that interfere with metabolism of sex steroids; smokers.

All EC dosing occurred during the follicular phase of the menstrual cycle and ingestion occurred under direct observation. Both the normal and obese BMI groups received a standard oral dose of EC (ECx1, 1.5 mg LNG; Next Choice™, Actavis Pharma, Parsippany, NJ). In a subsequent cycle following at least a one-cycle washout, the obese group received a double dose of EC (ECx2, 3.0 mg LNG). PK parameters were obtained via serum samples through an indwelling catheter at 0, 0.5, 1, 1.5, 2, and 2.5 h to evaluate the maximum serum LNG concentration (C_{max}). Total and Free LNG serum concentrations were measured at all time points. Estradiol (E2), LH, progesterone (P4), albumin, and sex hormone binding globulin (SHBG) were obtained once at the beginning of each PK visit.

2.1. Assay characteristics

Serum samples were assayed at the Endocrine Technologies Support Core (ETSC) at the Oregon National Primate Research Center (ONPRC, Beaverton, Oregon http://www.ohsu.edu/xd/research/centers-institutes/onprc/research-services/research-support/endocrine-technology.cfm). The ultra-high performance liquid chromatography-tandem triple quadrupole mass spectrometry (LC–MS/MS) assays utilized for this study were developed following the FDA's bioanalytical method validation including selectivity, accuracy, precision, recovery, calibration/standard curves, and stability. Total serum LNG levels were measured by (LC–MS/MS).One-hundred and fifty μl of serum