Comparison of vaginal and oral administration of emergency contraception

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Objective: To compare the physiologic effects of vaginally and orally administered emergency contraception.
Design: Prospective, open-label, crossover study.
Setting: University research center.
Patient(s): Nine regularly menstruating volunteers.
Intervention(s): Five subjects received 1,000 μg of levonorgestrel with 200 μg of ethinyl E_2 (twice the standard Yuzpe regimen dose) vaginally, and the standard Yuzpe regimen dose orally 1 week later. Four subjects received 1,500 μg of levonorgestrel (twice the standard Plan B regimen dose) vaginally and received the standard Plan B dose orally 1 week later. Serum samples were obtained at baseline and at frequent intervals after each dose.
Main Outcome Measure(s): Serum gonadotropin, hepatic globulin, and androgen levels measured at baseline, at the time of peak levonorgestrel, and 24 hours later.
Result(s): Gonadotropin, hepatic globulin, and androgen levels were suppressed to a similar degree among the four regimens, with a return to baseline levels after 24 hours.
Conclusion(s): We conclude that high doses of levonorgestrel found in emergency contraception regimens lead to a transient direct suppression of gonadotropin, hepatic globulin, and androgen levels. This effect is similar after vaginal and oral administration of emergency contraception. Therefore, the vaginal route of administration of emergency contraception regimens may be as efficacious as the oral route. (Fertil Steril® 2005;84:40–5. ©2005 by American Society for Reproductive Medicine.)

Key Words: Emergency contraception, vaginal administration, Yuzpe regimen, Plan B regimen, levonorgestrel, gonadotropins, androgens, hepatic globulins

The observation that postcoitally administered steroids may prevent conception has led to the development of so-called emergency contraceptive formulations. The Yuzpe regimen, containing both ethinyl E_2 (EE) and levonorgestrel, is the most commonly used emergency contraceptive (1). Although effective in preventing up to 75% of unwanted pregnancies with proper use, about 50% of treated women report nausea, and >20% vomit after ingesting the medications (2). Recently, Plan B, an oral progestin-only regimen containing a slightly higher dose of levonorgestrel, was found to be more effective than the Yuzpe regimen, with a lower incidence of nausea and vomiting. However, nausea was still present in 23% of cases, along with vomiting, dizziness, fatigue, headache, low abdominal pain, and diarrhea, which occurred in 5%–17% of patients (3). Vaginal, as opposed to oral, hormonal administration avoids exposure to the gastrointestinal tract as well as first-pass metabolism in the liver, while allowing a direct local effect of sex hormones on the endometrium (4–6).

The mechanism of action of orally administered emergency contraception is thought to be via a delay in ovulation with a possible direct action on the endometrium (7, 8). However, data regarding the effect of vaginally administered emergency contraception on pituitary gonadotropin secretion are lacking. Furthermore, despite being accepted as generally safe, data pertaining to acute effects of hepatic perfusion by high concentrations of orally and vaginally administered contraceptive steroids are also lacking. We have previously shown that low-dose combination oral contraceptives containing EE combined with levonorgestrel or norethindrone acetate suppress production of androgens, whereas sex hormone–binding globulin (SHBG) production is increased (9). However, data regarding effects of the substantially higher amounts of steroids present in emergency contraception on androgens are also lacking.

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The purpose of this study was to evaluate pharmacodynamic effects of the Yuzpe and Plan B regimens when administered vaginally, as compared with the oral route.

MATERIALS AND METHODS

The study received institutional review board approval and informed written consent was obtained from each volunteer before participation. Nine healthy women between the ages of 20–28 years with regular menses (25–35 days) volunteered to participate in the study. Subjects were excluded from participation if they were using any contraceptive hormones or if they had any contraindications to hormonal contraception, such as abnormal liver function, clotting disorders, or personal or family history of thromboembolic events. A negative urine pregnancy test was obtained from all subjects before administration of any study medications.

Participants were assigned to two treatment arms, with one group receiving the Yuzpe regimen (standard dose = 500 μg of levonorgestrel–100 μg of EE) and the second group receiving Plan B (standard dose = 750 μg of levonorgestrel). Five participants received twice the standard dose of the Yuzpe regimen vaginally, followed by the standard dose orally after a 1-week washout period. Four participants received twice the standard dose of Plan B vaginally, followed by the standard dose orally 1 week later. To minimize gastrointestinal side effects, a 50-mg oral tablet of dimenhydrinate (an anti-emetic) was ingested by each participant at the time of administration of study medications. Vaginally administered medications were placed in the posterior fornix of the vagina by the subjects themselves, following instruction from a physician. To minimize the possibility of tablets falling out of the vagina after administration of study medications, subjects remained in the hospital and were restricted to limited physical activity for the first 8 hours (sitting position for first 4 hours). None of the study participants reported any difficulty with vaginal retention of tablets (10). Each subject arrived in the fasting state in the midfollicular phase after completion of menses. Serum samples were obtained over a 24-hour period at baseline; then every 30 minutes for the first 4 hours; then at 5, 6, 8, 12, and finally 24 hours after oral or vaginal administration of the Yuzpe or Plan B regimens for measurement of levonorgestrel and EE and for calculation of their pharmacokinetic parameters, as described elsewhere (10). To ensure that study medications were administered in the follicular phase, serum P levels were obtained hourly for 6 hours and at 12 and 24 hours after administration of medications. All serum P values were <3.0 ng/mL.

Hormone and Globulin Assays

The following assay methods were used: LH and FSH were measured by direct chemiluminescent immunoassay (ACS180; Bayer, Tarrytown, NY); SHBG and DHEAS were measured by direct chemiluminescent immunoassay (Immulite analyzer, Diagnostic Products Corporation, Inglewood, CA); corticosteroid-binding globulin (CBG) and angiotensinogen were measured by highly specific direct RIA (intraassay coefficients of variation were 8.2%–9.6% and 7.3%–8.4%, respectively, and interassay coefficients of variation were 9.5%–10.9% and 8.1%–9.2%, respectively); androstenedione (A), T, and dihydrotestosterone were quantified by RIA with preceding organic solvent extraction and Celite column partition chromatography (11–14). Free T was calculated by a validated computer algorithm (15).

Statistical Analysis

Data were analyzed by using SPSS software (Statistical Package for the Social Sciences, version 10.0; SPSS, Inc., Chicago, IL). Because absorption of administered steroids varied among study participants, for the purpose of analysis, the measurements of LH, FSH, SHBG, CBG, angiotensinogen, A, T, free T, dihydrotestosterone, and DHEAS were individually adjusted and are reported at baseline and at the time of peak and nadir levonorgestrel levels (10). Serum hormone and globulin levels were compared among the four regimens by one-way analysis of variance. Spearman's correlation test was used for correlation analysis.

RESULTS

Overall, study medications were well tolerated. One subject reported nausea after vaginal administration of the Yuzpe regimen. A second subject reported nausea after both oral and vaginal administration of Plan B. Sleepiness was reported by all subjects for oral and vaginal administration of both regimens, consistent with the concomitant administration of dimenhydrinate. None of the subjects experienced vomiting, headache, vaginal irritation, or vaginal discharge.

Gonadotropins

Mean LH levels were at their lowest at the time of peak levonorgestrel for both Yuzpe and Plan B, with an average decrease of 27.0% and 8.1% for the vaginal and oral routes, respectively (P= not significant [NS]). Mean FSH levels at the time of peak levonorgestrel were lower than baseline for both vaginal and oral routes, with an average percentage decrease of 5.6% and 11.2%, respectively (P=NS). There was no significant difference in mean LH or FSH values between Yuzpe and Plan B regimens administered orally or vaginally. There was a statistically significant inverse correlation between LH and levonorgestrel levels ($r = -0.45$; $P<.05$), as well as FSH and levonorgestrel levels ($r = -0.61$; $P<.05$) in the vaginally administered regimens (Figs. 1 and 2).

Hepatic Globulins

At peak levels of levonorgestrel, mean levels of angiotensinogen (1,059 ± 529 pg/mL), CBG (3.5 ± 2.6 mg/dL), and SHBG (40.1 ± 17.7 nmol/L) were consistently at their lowest with any given regimen, with a mean percentage