

Original research article

Bioavailability of the Yuzpe and levonorgestrel regimens of emergency contraception: vaginal vs. oral administration

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Abstract

Separate crossover studies compared the bioavailability of oral vs. vaginal routes of administration for the Yuzpe ($n=5$) and levonorgestrel regimens ($n=4$) of emergency contraception. Twice the standard dose of the Yuzpe regimen (200 μg of ethinyl estradiol, 1000 μg of levonorgestrel) or the levonorgestrel regimen (1500 μg of levonorgestrel) was self-administered vaginally. One week later, each subject received orally the standard dose of the assigned medication. Serial blood samples were collected over 24 h and assayed for levonorgestrel and ethinyl estradiol (for the Yuzpe regimen only). Paired t tests were used to compare oral vs. vaginal administration for maximum concentration (C_{max}), time to maximum concentration (T_{max}) and area under the curve over 24 h (AUC_{0-24}). Relative bioavailability (vaginal/oral) was derived from AUC_{0-24} . Vaginal administration of double the standard dose of the Yuzpe regimen resulted in a lower C_{max} (vaginal=5.4 vs. oral=14.6 ng/mL, $p=.038$) and a later T_{max} (5.9 vs. 2.0 h, $p=.066$) for levonorgestrel, compared to oral administration. Corresponding ethinyl estradiol concentrations were higher (786 vs. 391 pg/mL, $p=.039$) and peaked later (4.0 vs. 1.9 hr, $p=.154$) with vaginal administration. Relative bioavailabilities for levonorgestrel and ethinyl estradiol were 58% and 175%, respectively. Similarly, vaginal administration of the levonorgestrel regimen resulted in a lower C_{max} (vaginal=5.4 vs. oral=15.2 ng/mL, $p=.006$) and a later T_{max} (7.4 vs. 1.3 h, $p=.037$) for levonorgestrel, compared to oral administration. The relative bioavailability was 62%. Our preliminary data suggest that vaginal administration of these emergency contraception regimens appears to require at least three times the standard oral dose to achieve equivalent systemic levonorgestrel concentrations.

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1. Introduction

The most widely used emergency contraception (EC) methods in the world are the Yuzpe regimen (combined estrogen–progestin contraceptive pills) and the levonorgestrel (LNG) regimen (progestin only) [1]. The Yuzpe regimen was developed in 1977 [2] and later compared to the LNG regimen in clinical trials [3,4]. In the largest randomized trial to date, the LNG regimen has been shown to be more effective and associated with fewer side effects than the Yuzpe regimen [4].

Vomiting occurs in about 5.6% of women taking the LNG regimen compared to about 18.8% for the Yuzpe regimen [4]. The management of vomiting shortly after taking EC is not well defined. In severe cases or if the pills are visible in the emesis, a replacement dose given vaginally may be warranted. Vaginal placement of oral contraceptives has been associated with lower circulating steroid levels compared to oral administration [5,6]. Alvarez et al. [5] found that the plasma levels of levonorgestrel with vaginal administration of the pill were about one half of the levels achieved when the same pills were taken orally.

The objective of the present study was to compare the pharmacokinetics between oral and vaginal routes of administration of both the Yuzpe (500 μg LNG, 100 μg EE) and levonorgestrel regimens (750 μg LNG) of EC. The

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vaginal dosages were double that of the standard oral dosages, with the expectation of achieving similar circulating steroid levels.

2. Methods and materials

Ten healthy women volunteered for pilot studies measuring the bioavailability of the active ingredients of two EC regimens. Reasons for exclusion included a history of irregular menstrual cycles, current use of any hormonal contraception, contraindications to hormonal contraception including impaired liver function, blood clotting disorders, family or personal history of venous thromboembolism or pulmonary embolism and intolerance to oral contraceptives. The protocol was approved by the Queen's University/Kingston General Hospital Research Ethics Board and written informed choice was obtained from all participants.

Five subjects were enrolled into the Yuzpe regimen study and another five were enrolled into the LNG regimen study. During the prior 2 weeks, subjects stopped any hormonal contraception and started nonhormonal methods of pregnancy protection. Each participant arrived fasting at 0700 hours after cessation of menstruation in the mid-follicular phase. Pregnancy was excluded by means of a negative urine pregnancy test. A saline lock was inserted and the first 5 cm³ blood sample was drawn. Four tablets of a combination contraceptive pill (Yuzpe regimen) containing 200 µg of ethinyl estradiol (EE) and 1000 µg of LNG, or two tablets of a progestin-only contraceptive pill (LNG regimen) containing 1500 µg of LNG, were placed in the posterior fornix of the vagina by the subjects themselves. These doses were double the standard doses for EC. Subjects remained in hospital and limited physical activity for the first 8 h to minimize the tablet falling out of the vagina. One week later, each subject received the standard dose of the assigned medication by the oral route. On each occasion, an antiemetic (Gravol, Carter-Horner, Mississauga, Ontario, Canada) containing 50 mg of dimenhydrinate was coadministered.

Fourteen serial blood samples were collected over a 24-h period; at time 0, then every half hour for the first 4 h, then at 5, 6, 8, 12 and 24 h. Separated plasma was stored at –20° until analysis by radioimmunoassay. Samples collected after administration of the Yuzpe regimen were assayed for LNG and EE. Samples collected after administration of the LNG regimen were assayed for LNG. A single progesterone measurement was obtained during vaginal administration of both regimens to confirm a follicular phase endometrium.

The specific radioimmunoassay (RIA) protocols for LNG and EE have been previously described [7,8]. Steroids were extracted with ethyl acetate/hexane (3:2). Tritiated internal standards were added to each sample to correct for procedural losses. Each RIA used specific antisera in conjunction with iodinated radioligands, and separation of the unbound steroid was achieved by a second antibody. The sensitivities of LNG and EE were 0.05 ng/mL and 15 pg/mL,

respectively. Intra-assay and interassay coefficients of variation for LNG were 4.4% and 8.9%, respectively. The respective coefficients for EE were 6.9% and 11.0%. Progesterone was measured in a single batch using a Coat-A-Count ¹²⁵I radioimmunoassay kit (Diagnostic Products, Los Angeles, CA). The duplicate standard curve ranged from 0.1 to 40 ng/mL. The detection limit was approximately 0.02 ng/mL. Highly specific antiserum was used with a low cross-reactivity to other naturally occurring steroids.

2.1. Pharmacokinetic measures

Summary measures of the time concentration curve included maximum concentration (C_{max}), time to maximum concentration (T_{max}) and area under the curve over 24 h (AUC_{0-24}), calculated using the trapezoidal rule [9]. Relative bioavailability (vaginal/oral) was derived from AUC_{0-24} and corrected for dose by multiplying by 1/2. The coefficient of variation, expressing sample variation relative to the mean, was calculated for relative bioavailability. The mean, SD and range were calculated for the other summary measures. Paired *t* tests were used to compare oral vs. vaginal administration for each measure, and 95% confidence intervals (CI) were calculated for these differences. Descriptive and inferential statistics were generated using SPSS (version 10). The sample size in each study was less than the minimum of 12 required for bioequivalence testing [10]. Probability values are reported in the context that type II errors (false-negative results) were probable.

3. Results

3.1. Demographics

Demographics for the five subjects who completed both arms of the Yuzpe regimen study and for the four subjects who completed both arms of the LNG regimen study are provided in Table 1. One woman dropped out of the LNG regimen study after the first period (vaginal administration) for personal reasons. A follicular phase endometrium was confirmed for each individual with a progesterone level less than 3 ng/mL during vaginal administration of the respective EC regimen [11].

3.2. Pharmacokinetics for the Yuzpe regimen

Mean plasma LNG concentrations plus SD over 24 h, after oral and vaginal administration of the Yuzpe regimen in five subjects, are shown in Fig. 1. There was marked

Table 1
Demographics for subjects studied on the Yuzpe regimen and levonorgestrel regimen

Parameter	Yuzpe regimen (<i>n</i> =5), mean (range)	Levonorgestrel regimen (<i>n</i> =4), mean (range)
Age (years)	21.8 (21–24)	24.3 (20–28)
BMI (kg/m ²)	26 (21–31)	25 (23–27)
Cycle length (days)	28 (25–31)	27 (27–28)

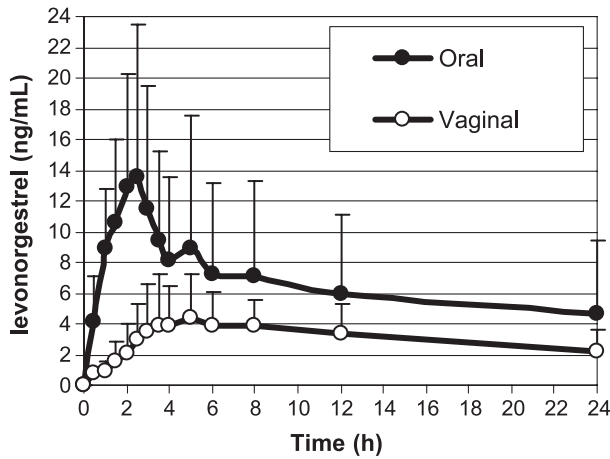


Fig. 1. Mean plasma levonorgestrel concentrations (+SD) over 24 h after oral and vaginal administration of the Yuzpe regimen in five subjects. Oral dose=500 µg levonorgestrel, 100 µg ethinyl estradiol. Vaginal dose equaled two times the oral dose.

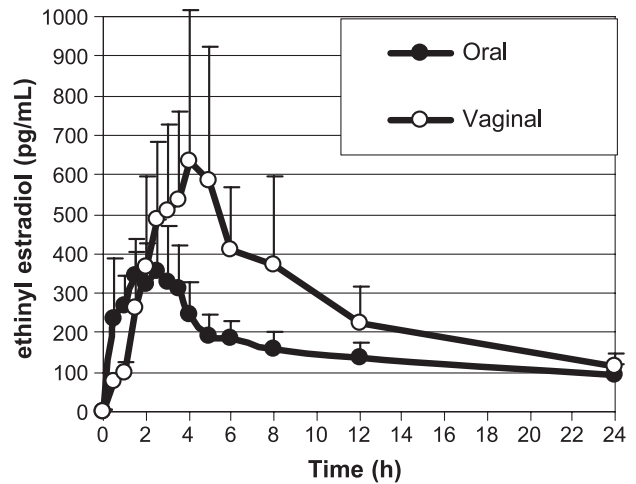


Fig. 2. Mean plasma ethinyl estradiol concentrations (+SD) over 24 h after oral and vaginal administration of the Yuzpe regimen in five subjects. Oral dose=500 µg levonorgestrel, 100 µg ethinyl estradiol. Vaginal dose equaled two times the oral dose.

intersubject variability in LNG concentrations particularly for oral administration. Mean LNG values for C_{max} , T_{max} and AUC_{0-24} are presented in Table 2. On average, vaginal administration of double the dose resulted in a lower peak response by 9.2 ng/mL (95% CI=0.8 to 17.7; $p=.038$, paired t test), a delay in the time-to-peak response by 3.9 h (95% CI=−0.4 to 8.2; $p=.066$, paired t test) and a decreased AUC by 85.2 ng h/mL (95% CI=−29.9 to 200.3; $p=.109$, paired t test) compared to oral administration.

Mean plasma EE concentrations (+SD) over 24 h, after oral and vaginal administration of the Yuzpe regimen in five subjects, are shown in Fig. 2. There was marked intersubject variability in EE concentrations, particularly for vaginal administration. Mean EE values for C_{max} , T_{max} and AUC_{0-24} are presented in the bottom half of Table 2. On average, vaginal administration at double the dose resulted in a higher peak response by 395 pg/mL (95% CI=34 to 756; $p=.038$, paired t test), a delayed time-to-peak response by 2.1 h (95% CI=−1.2 to 5.4; $p=.154$, paired t test) and a

greater AUC by 2578 pg h/mL (95% CI=747 to 4409; $p=.017$, paired t test), compared to oral administration.

The mean relative bioavailability (AUC_{0-24} vaginal/oral) of LNG for the Yuzpe regimen was 58%, with a coefficient of variation equal to 34%. Correcting for dose, the relative bioavailability equaled 29%. The mean relative bioavailability (AUC_{0-24} vaginal/oral) of EE for the Yuzpe regimen was 175%, with a coefficient of variation equal to 30%. Correcting for dose, the relative bioavailability equaled 88%.

3.3. Pharmacokinetics for the levonorgestrel regimen

Mean plasma LNG concentrations (+SD) over 24 h, after oral and vaginal administration of the LNG regimen in four subjects, are shown in Fig. 3. Compared to the Yuzpe regimen, less intersubject variability in LNG concentrations

Table 2
Pharmacokinetic parameters measured in five subjects for oral and vaginal administration of the Yuzpe regimen

	Oral		Vaginal (double the dose)	
	Mean (SD)	Range	Mean (SD)	Range
<i>Levonorgestrel</i>				
C_{max} (ng/mL)	14.6 (9.2)	6.5–28.7	5.4 (2.5)	3.3–9.6
T_{max} (h)	2.0 (0.6)	1.0–2.5	5.9 (3.6)	3.0–12.0
AUC_{0-24} (ng h/mL)	158.0 (129.1)	48.9–356.0	72.8 (37.2)	39.9–131.9
<i>Ethinyl estradiol</i>				
C_{max} (pg/mL)	391 (123)	183–506	786 (286)	528–1275
T_{max} (h)	1.9 (1.0)	0.5–3.0	4.0 (2.3)	2.5–8.0
AUC_{0-24} (pg h/mL)	3874 (1017)	2216–4865	6452 (1483)	4776–8274

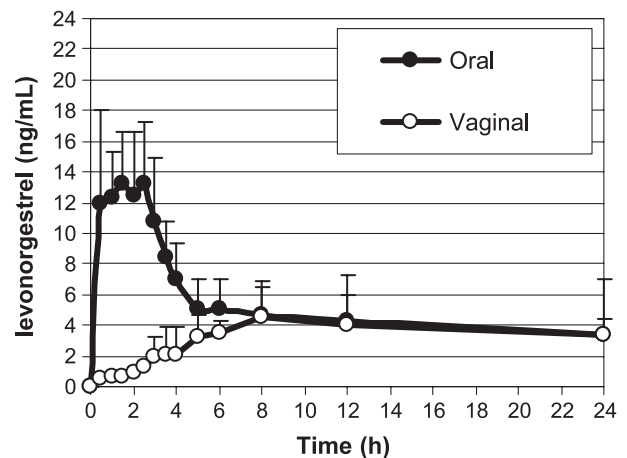


Fig. 3. Mean plasma levonorgestrel concentrations (+SD) over 24 h after oral and vaginal administration of the levonorgestrel regimen in four subjects. Oral dose=750 µg levonorgestrel. Vaginal dose equaled two times the oral dose.

Table 3
Pharmacokinetic parameters measured in four subjects for oral and vaginal administration of the levonorgestrel regimen

Levonorgestrel	Oral		Vaginal (double the dose)	
	Mean (SD)	Range	Mean (SD)	Range
C_{\max} (ng/mL)	15.2 (3.9)	9.4–17.3	5.4 (2.4)	2.9–8.7
T_{\max} (h)	1.3 (0.6)	0.5–2.0	7.4 (3.6)	3.5–12.0
AUC_{0-24} (ng h/mL)	127.7 (41.0)	73.6–163.0	80.8 (51.0)	40.6–153.9

was observed for both oral and vaginal administration. Mean LNG values for C_{\max} , T_{\max} and AUC_{0-24} are presented in Table 3. On average, vaginal administration of double the dose resulted in a lower peak response by 9.8 ng/mL (95% CI=5.5 to 14.1; $p=.006$, paired t test), a delayed time-to-peak response by 6.1 h (95% CI=0.7 to 11.6; $p=.037$, paired t test) and a decreased AUC by 46.9 ng h/mL (95% CI=–17.2 to 111.0; $p=.102$, paired t test) compared to oral administration.

The mean relative bioavailability (AUC_{0-24} vaginal/oral) of LNG for the LNG regimen was 62% with a coefficient of variation equal to 41%. Correcting for dose, the relative bioavailability equaled 31%.

4. Discussion

To the best of our knowledge, the present studies are the first to measure steroid pharmacokinetics for the Yuzpe and LNG regimens of EC following vaginal and oral administration. These preliminary data provide vital information for designing future clinical and pharmacologic studies with sufficient power. Present comparative data on LNG bioavailability for contraceptive pills are limited [5,12]. Alvarez et al. [5] measured LNG concentrations in six women following vaginal and oral administration of a combined oral contraceptive pill (500 μ g DL-norgestrel, 50 μ g EE). They showed that plasma levels of LNG after the vaginal route of pill administration were about one-half the levels achieved when the same pills were taken orally. The authors commented that “without attempts to adjust the dose administered in order to achieve plasma levels of levonorgestrel comparable to those achieved with oral administration, it was possible to suppress ovulation in five of the six vaginal treatment cycles.”

Back et al. [12] studied the pharmacokinetics of LNG and EE in five women following intravenous (iv), oral and vaginal administration of a combined oral contraceptive pill (250 μ g LNG, 50 μ g EE). They concluded that the overall bioavailability was not reduced for either steroid when a single tablet was inserted into the vagina. The fractional bioavailability estimates quoted in their study were derived from AUC (oral/iv) and AUC (vaginal/iv), which indicate absolute bioavailability. Area under the curve (vaginal/oral) measures calculated from the raw data give relative bioavailabilities of 87% for LNG and 120% for EE.

Our results showed relative bioavailabilities for LNG (corrected by dose) of 29% and 31% for the Yuzpe and LNG regimens, respectively. The relative bioavailability for EE (corrected by dose) for the Yuzpe regimen was 88%. Disparities in relative bioavailabilities between the current report and past studies could be due to differences in pill formulations, steroids (DL-norgestrel vs. levonorgestrel), doses, vaginal administration protocols, radioimmunoassay methods or phases of the menstrual cycle. In the study by Back et al. [12], subjects remained seated for 4 h after vaginal administration of a combination oral contraceptive pill containing 250 μ g of LNG and 50 μ g of EE during the luteal phase. A recent study on the pharmacokinetics following oral administration of a single 750 μ g LNG tablet in 16 women resulted in a C_{\max} of 14.1 ng/mL, a T_{\max} of 1.6 h and an AUC_{0-80} of 111.9 ng h/mL [13]. High-resolution gas chromatography with negative ionization mass spectrometric detection was used to determine these measures, which are similar in magnitude to those reported here.

The mechanisms of action for both the Yuzpe and LNG regimens of EC are not well understood [1,14], and efficacy studies are inexact by design [1]. Our best evidence indicates that the proportion of pregnancies prevented (compared with the expected number without treatment) is about 85% for the LNG regimen compared to 57% for the Yuzpe regimen [4]. A meta-analysis of eight studies including the WHO study of 1998 (Task Force 1998) concludes that when used within 72 h after sex, the Yuzpe regimen prevents about 74% of expected pregnancies [15].

There is concern about decreased absorption and contraceptive effectiveness subsequent to vomiting shortly after taking EC [16,17]. The *American College of Obstetricians and Gynecologists Practice Bulletin* on emergency oral contraception states that “there is no evidence on which to base a recommendation for repeating the dose if emesis occurs. However, it seems reasonable to infer that if gastrointestinal symptoms are estrogen mediated secondary to an effect on the central nervous system, absorption of the dose should have occurred by the time of emesis” ([18], p. 3). Others have recommended repeating the dose, if vomiting occurs within 1 h of the administration of medication [19]. We found that maximum blood levels of LNG are reached in about 1.3 h after oral consumption of the LNG regimen.

In the situation where a woman is unable to take EC orally; if severe vomiting occurs or the pills are visible in the emesis, vaginal administration is an option [1,6]. Our preliminary data suggest that at least three times the standard oral dose of current EC regimens is required with vaginal administration to achieve equivalent systemic levonorgestrel concentrations.

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