# Bioequivalence Study of Postcoital Emergency Contraceptions Containing Levonorgestrel

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***Objective :*** *The progestogen-only method of emergency contraception, levonorgestrel, is one of the effectiveness in preventing expected pregnancies. The comparative bioavailability was carried out on levonorgestrel tablets (0.75 mg) from two different sources (Hungarian and Thai made).*
***Method :*** *Eighteen healthly female volunteers were given a single oral dose of 0.75 mg tablets in a crossover design. Serum levonorgestrel concentration was determined by radio-immunoassay. The pharmacokinetic analysis of serum levonorgestrel concentration from each treatment was established. The comparative bioavailability of the two products was determined by the analysis of variance (ANOVA) for two way crossover design.*
***Results :*** *The results found that the mean peak (X±SD)serum concentration ($C_{max}$) of the Thai –made pill and Hungarian-pill were 1.18 ± 0.12 and 1.14 ± 0.10 ng/ml, respectively. The 90% confidence interval for the difference of log $C_{max}$ mean was 99.54 – 120.78%. The time to peak serum concentration ($T_{max}$) of the Thai-made pill and Hungarian-pill were 1.56 ± 0.73 and 1.58 ± 0.67 hrs, respectively. The different time of peak serum levonorgestrel concentration was 1.27%. The mean area under the curve (AUC) of Thai-made pill and Hungarian-pill were 2.14 ± 0.21 and 2.09 ± 0.16 ng.h/ml, respectively. The 90% confidence interval for the difference of log AUC mean was 103.27 – 121.89%.*
***Conclusion :*** *The persent study revealed that the 90% confidence interval for the difference of log $C_{max}$ mean and log AUC mean were in the criteria of acceptance, which should be within 80-125%. So, the authors can conclude that the Thai- made pill was bioequivalent to the Hungarian-pill.*

***Keywords :*** *Bioequivalence, Postcoital contraception, Emergency contraception, Levonorgestrel.*

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There are various choices for Thai women to access contraceptions eg. oral pills, IUD, injectable, implant, etc. While most contraceptives are appropriate for use before sexual intercourse. A WHO controlled trial found a progestogen-only method of emergency contraception to be considerably more effective in preventing expected pregnancies than the Yuzpe regimen [1].

The progestin-only emergency contraceptives [2] consist of 0.75 mg levonorgestrel taken in two doses of twelve hours apart and started within 48 hours of unprotected intercourse. The mechanism for prevention of pregnancy is unclear. It is believed this regimen has a high dose of progestin. It will increase the movement of the fallopian tubes, or may change the endometrium not suitable for fertilized ovum. In most of the cases, it does not inhibit ovulation [3,4] .

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In a multicenter trial conducted by the World Health Organization, the observed failure rate per treated cycle of 0.75 mg levonorgestrel was 0.8% [5]. This rate is similar to that of other reports for postcoital emergency contraception [6,7] . Bleeding and spotting are the most reported adverse events. Other side effects are headache, dizziness and nausea [8-13].

In this randomized crossover study, two types of 0.75 mg levonorgestrel tablets were compared. Postinor (Gedeon Richter Ltd, Hungary) which is registered for postcoital contraception in several countries, and a comparable levonorgestrel pill produced in Thailand (Brywood Pharmaceutical Ltd.). The present paper described a comparative bioavailability of these two types of tablets. The objective was to determine whether the Thai-made pill has a comparable efficacy to its innovator's product (the Hungarian-pill).

## Material and Method

Eighteen normal and healthy female volunteers, aged between 21-40 years, were recruited in the study. All subjects had regular menstrual cycles (28±7 days) and did not use any steroidal agents nor lactated for at least three months prior to the admission. No other drugs were taken during the study. A medical history and physical examination were taken from each subject before entering the study. Normal liver and kidney function were confirmed by routine laboratory test. All subjects were negative for HIV and hepatitis B infection. The study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University, Thailand. Informed consent was obtained from each of the volunteers.

This was a randomized, double-blind, crossover study. Each subject was randomly assigned to receive a single dose of 0.75 mg levonorgestrel orally (either the Hungarian-pill or Thai-made pill) in the morning after an overnight fast and remained fast for at least 2 hours after drug administration. Soft drink and lunch were allowed after receiving the study drug for 2-hours and 4-hours, respectively. Meal and fluid intake were identical for the study period. Neither alcohol nor caffeine containing beverage was allowed during the study period. Blood samples were collected from antecubital vein immediately before and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 10 and 24 hour after dosage administration. Blood samples were allowed to clot at room temperature for at least 30 minutes and then centrifuged. The separated serum samples were stored at -20 C until analysed. At least 1 week after the previous visit, subjects had crossover to receive the different levonorgestrel preparation.

Concentrations of levonorgestrel in the serum samples were quantifed by radioimmuno assay[14]. The intraday and inter-day precision were validated. The % coefficient of variation (%CV) for intraday and inter-day was not more than 15% and 20%, respectively. This method was also validated for accuracy and sensitivity.

The pharmacokinetic analysis of individual serum levonorgestrel concentration from each treatment was established by the graphing method. The peak serum concentration ($C_{max}$) and time to peak serum concentration ($T_{max}$) were directly observed from the data. The area under the serum concentration-time curve ($AUC_{0-\infty}$) was calculated using the linear trapezoidal rule and extended to infinite time[15].

Comparative bioavailability of the Thai-made product relative to the Hungarian-product was assessed by using the relevant pharmacokinetic parameters, $C_{max}$ and $AUC_{0-\infty}$. Both parameters were transformed to logarithmic scale for statistical analysis. The difference of the corresponding log $C_{max}$ and log $AUC_{0-\infty}$ between the two products were determined by analysis of variance (ANOVA) for two way crossover design[16] at the significant level 0.05.

The 90% confidence interval (two-one-sided tests) for the differences of $C_{max}$ and $AUC_{0-\infty}$ means based on log transformed data were calculated[17].

### *Acceptance Criteria* [15, 18, 19]

The two products were considered to be of bioequivalence when each 90% confidence interval was within 80-125%

## Results

Eighteen female subjects, average mean age was 33.4 years ranged 24-40 years. Their average body weight and height were 53.9 kg and 157.9 cm, respectively. Their average Body Mass Index (BMI) was 21.6. All subjects had regular menstrual cycles.

The values for serum levonorgestrel concentrations of the two products were shown in Table 1 and Table 2 and mean concentration-time curve were plotted in Fig. 1.

Absorption was rapid in most subjects and maximum serum concentrations levonorgestrel were achieved in less than 2 hours in fifteen women after oral intake of both products. Serum concentrations in all subjects were slightly higher when taking Thai-made pill (Fig. 1).

The pharmacokenetic parameters used for the evaluation of bioequivalence between Thai-made pill and Hungarian pill were the peak serum levonorgestrel

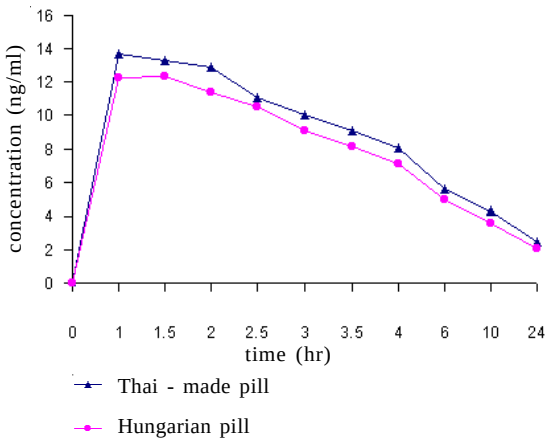


**Fig. 1** Mean serum levonorgestrel concentration-time curve in 18 subjects after oral intake of 0.75 mg tablets of the Thai-made pill and the Hungarian pill

**Table 1.** Serum levonorgestrel concentration (ng/ml) in 18 subjects after oral intake of 0.75 mg of levonorgestrel of the Thai-made pill

| Subject No. | Time (hr) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 | 6 | 10 | 24 |
| 1 | 9.00 | 14.07 | 16.04 | 11.79 | 8.55 | 7.69 | 7.38 | 4.91 | 3.82 | 1.92 |
| 2 | 15.22 | 9.09 | 6.80 | 7.54 | 5.08 | 4.60 | 4.01 | 2.94 | 1.68 | 1.43 |
| 3 | 10.72 | 13.38 | 12.60 | 10.82 | 11.40 | 7.45 | 4.54 | 3.96 | 3.10 | 1.53 |
| 4 | 21.67 | 21.78 | 21.77 | 19.92 | 16.33 | 15.94 | 14.24 | 12.21 | 10.97 | 6.37 |
| 5 | 16.78 | 14.11 | 11.93 | 9.80 | 8.38 | 7.74 | 7.52 | 4.63 | 3.75 | 1.90 |
| 6 | 12.11 | 16.53 | 14.50 | 10.88 | 12.81 | 14.10 | 10.66 | 8.33 | 6.87 | 3.72 |
| 7 | 14.98 | 17.68 | 16.48 | 15.30 | 14.24 | 13.31 | 11.52 | 10.80 | 5.46 | 3.78 |
| 8 | 15.05 | 10.30 | 11.76 | 10.67 | 11.46 | 16.03 | 13.87 | 8.40 | 7.66 | 4.05 |
| 9 | 12.45 | 14.43 | 14.85 | 11.64 | 9.32 | 9.52 | 8.56 | 4.93 | 5.23 | 2.11 |
| 10 | 18.03 | 14.47 | 15.88 | 13.36 | 11.87 | 9.43 | 9.15 | 7.66 | 5.04 | 3.18 |
| 11 | 21.10 | 16.76 | 15.95 | 12.04 | 10.55 | 8.60 | 7.61 | 4.83 | 4.90 | 3.47 |
| 12 | 18.31 | 15.43 | 10.93 | 9.96 | 9.45 | 6.70 | 6.66 | 4.00 | 3.33 | 1.92 |
| 12 | 3.37 | 4.62 | 8.48 | 11.12 | 11.87 | 10.06 | 10.48 | 4.67 | 3.03 | 1.74 |
| 14 | 10.18 | 12.18 | 10.40 | 8.65 | 8.52 | 8.02 | 7.34 | 5.84 | 3.46 | 2.33 |
| 14 | 10.37 | 11.53 | 12.07 | 10.40 | 9.96 | 6.45 | 6.20 | 4.46 | 2.92 | 2.08 |
| 16 | 6.66 | 6.56 | 6.61 | 5.75 | 4.81 | 3.47 | 3.65 | 0.99 | 0.92 | 0.67 |
| 17 | 12.54 | 11.08 | 10.06 | 7.87 | 5.80 | 5.73 | 4.41 | 2.72 | 1.78 | 0.93 |
| 18 | 18.39 | 17.93 | 14.53 | 12.14 | 9.62 | 8.63 | 7.38 | 4.67 | 3.77 | 1.65 |
| Mean | 13.66 | 13.27 | 12.87 | 11.09 | 10.00 | 9.08 | 8.07 | 5.61 | 4.32 | 2.49 |
| SD | 4.84 | 4.07 | 3.81 | 3.11 | 3.01 | 3.62 | 3.13 | 2.85 | 2.40 | 1.38 |

**Table 2.** Serum levonorgestrel concentration (ng/ml) in 18 subjects after oral intake of 0.75 mg of levonorgestrel of the Hungarian pill

| Subject No. | Time (hr) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 | 6 | 10 | 24 |
| 1 | 11.72 | 12.85 | 10.98 | 9.63 | 11.28 | 9.64 | 6.85 | 6.18 | 4.80 | 2.37 |
| 2 | 14.65 | 12.33 | 10.73 | 9.81 | 6.87 | 5.43 | 5.71 | 3.58 | 3.22 | 2.31 |
| 3 | 11.22 | 10.07 | 9.05 | 7.10 | 6.81 | 5.53 | 4.68 | 4.39 | 2.89 | 1.75 |
| 4 | 22.53 | 19.92 | 17.78 | 14.48 | 12.64 | 11.13 | 9.69 | 6.54 | 5.69 | 3.49 |
| 5 | 13.60 | 13.70 | 10.56 | 10.73 | 9.50 | 10.15 | 7.87 | 4.85 | 3.19 | 1.79 |
| 6 | 19.99 | 16.97 | 14.82 | 12.84 | 13.52 | 9.52 | 9.14 | 8.00 | 6.36 | 3.44 |
| 7 | 14.95 | 18.27 | 16.18 | 16.01 | 12.60 | 11.23 | 9.61 | 8.69 | 6.33 | 3.81 |
| 8 | 6.33 | 12.68 | 12.62 | 12.22 | 13.20 | 12.93 | 11.06 | 6.06 | 5.25 | 3.50 |
| 9 | 12.19 | 11.78 | 11.32 | 10.50 | 8.56 | 8.04 | 7.64 | 4.46 | 3.31 | 1.63 |
| 10 | 15.91 | 16.25 | 11.12 | 7.45 | 1.48 | 2.32 | 3.04 | 4.61 | 2.64 | 1.72 |
| 11 | 12.66 | 11.00 | 13.37 | 11.82 | 9.36 | 7.76 | 7.34 | 5.19 | 4.61 | 2.45 |
| 12 | 9.18 | 9.69 | 7.16 | 6.28 | 5.53 | 5.55 | 3.99 | 2.31 | 2.08 | 1.49 |
| 12 | 3.04 | 5.07 | 10.06 | 9.30 | 8.25 | 6.82 | 6.35 | 2.87 | 1.91 | 1.32 |
| 14 | 5.16 | 6.64 | 8.96 | 13.01 | 13.89 | 12.52 | 11.29 | 5.64 | 4.66 | 2.25 |
| 14 | 14.06 | 13.43 | 10.44 | 9.03 | 7.69 | 6.16 | 5.85 | 4.20 | 2.28 | 1.74 |
| 16 | 8.70 | 9.50 | 7.78 | 6.63 | 4.42 | 4.68 | 3.85 | 2.26 | 1.41 | 0.89 |
| 17 | 16.18 | 14.08 | 11.73 | 9.84 | 7.86 | 6.41 | 5.16 | 3.27 | 1.65 | 0.57 |
| 18 | 8.56 | 7.97 | 10.57 | 12.32 | 10.05 | 9.58 | 8.58 | 6.23 | 2.88 | 1.17 |
| Mean | 12.26 | 12.34 | 11.40 | 10.50 | 9.08 | 8.08 | 7.09 | 4.96 | 3.62 | 2.09 |
| SD | 4.97 | 3.39 | 2.74 | 2.71 | 3.41 | 2.93 | 2.47 | 1.80 | 1.60 | 0.95 |

concentration ($C_{max}$), the time to peak serum levonorgestrel concentration ($T_{max}$), and the area under the serum levonorgestrel concentration-time curve ($AUC_{0-\infty}$). All these parameters were derived from individual serum levonorgestrel concentration-time profile. Their mean values were summarized in Table 3.

Table 3 shows the mean pharmacokinetic parameters ( $\bar{X}\pm SD$ ) of levonorgestrel in 18 subjects

**Table 3.** Mean pharmacokinetic parameters ($\bar{X}\pm SD$) of levonorgestrel in 18 subjects after oral intake of 0.75 mg of levonorgestrel of Thai-made pill and Hungarian pill

| Parameters | Thai-made pill | Hungarian pill | 90% Confidence Interval of Mean Differences |
|---|---|---|---|
| $C_{max}$ (ng/ml) | 1.18 ± 0.12* | 1.14 ± 0.10* | 99.54-120.78 |
| $T_{max}$ (hr) | 1.56 ± 0.73** | 1.58 ± 0.67** | |
| $AUC_{0-\infty}$ (ng.h/ml) | 2.14 ± 0.21* | 2.09 ± 0.16* | 103.27-121.89 |

n = 18 * Log transformed data ** Observed data

after oral intake of 0.75 mg of levonorgestrel of the Thai-made pill and Hungarian pill.

The mean $C_{max}$ of the Thai-made pill and Hungarian pill were 1.18 ± 0.12 ng/ml and 1.14 ± 0.10 ng/ml, respectively. The 90% confidence interval of difference of $C_{max}$ mean (log transformed data) was 99.54-120.78%.

The mean $AUC_{0-\infty}$ of the Thai-made pill and Hungarian pill were 2.14 ± 0.21 ng.hr/ml and 2.09 ± 0.16 ng.hr/ml, respectively. The 90% confidence interval of difference of $AUC_{0-\infty}$ mean (log transformed data) was 103.27-121.89%.

The mean $T_{max}$ of the Thai-made pill and Hungarian pill were 1.56 ± 0.73 hr and 1.58 ± 0.67 hr, respectively. The difference of time of peak serum levonorgestrel concentration in the present study was 1.27% which was in criteria which is not more than 20%.

## Discussion

"Levonorgestrel regimen" is the new choice for emergency contraception. The popularity among Thai youths has increased more than the Yuzpe regimen. Women in the levonorgestrel group reported less nausea, vomiting, dizziness and fatigue which were the undesirable estrogenic side effects of the Yuzpe regimen. But the menstrual disturbance was similar for the two regimens.[10,13]

In Thailand, the contraceptive needs of young couples for unprotected intercourse frequently occurs. Often, contraception is used but is inadequate or fails. When this happens, emergency contraception is the last chance to prevent unwanted pregnancies. Increased access to and appropriate use of emergency contraception would reduce both the number of unwanted pregnancies and the number of pregnancies terminated.

In the present study two types of levonorgestrel tablets, the Thai-made pill and Hungarian-pill, were used in a comparative bioavailability trial. The results showed that the Thai-made pill had a slightly greater bioavailability as judged from slightly higher plasma concentrations of levonorgestrel and slightly larger area under the plasma concentration-time curve. It would suggest that the amount of levonorgestrel in the Thai-made pill may be in excess of what is needed. The blood concentration values at different times in 24 hours of 0.75 mg levonorgestrel in both two types were comparable with the blood values from the levonorgestrel tablet studied by Shi YE et al[11].

In conclusion, the pharmacokinetic parameters and the bioequivalence testing of 0.75 mg levonorgestrel of the Thai-made pill and Hungarian pill were conducted in the present study. The results demonstrated bioequivalence of the two products concerning the rate ($C_{max}$) and extent ($AUC_{0-\infty}$) of absorption. The parametric 90% confidence intervals and estimates of the mean difference of these parameters were well within the acceptable range of 80-125%, based on standard bioeqiuvalence guidelines. Therefore, generic levonorgestrel (the Thai-made pill) preparation possessed a high probability practical equivalence as the innovator's product (Hungarian pill).

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## การศึกษาชีวสมมูลของยาคุมฉุกเฉินหลังร่วมเพศที่ประกอบด้วยฮอร์โมนลีโวนอร์เจสเตรล

**สุมนา ชมพูทวีป, สมัย ลีพิพัฒน์ไพบูลย์**

***วัตถุประสงค์*** *: เพื่อศึกษายาคุมกำเนิดฉุกเฉินหลังร่วมเพศที่ผลิตขึ้นในประเทศไทยมีประสิทธิภาพในการรักษาเท่าเทียมกับยาต้นแบบที่ผลิตจากประเทศฮังการี โดยใช้วิธีการศึกษาเปรียบเทียบผลทางเภสัชจลนศาสตร์ ของยาทั้งสองชนิด*

***วัสดุและวิธีการ*** *: เป็นการศึกษาทางคลินิกเชิงทดลองแบบข้ามเชิงสุ่ม โดยดำเนินการศึกษาที่ภาควิชาเภสัชวิทยา และภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย อาสาสมัครสตรี 18 คน อายุระหว่าง 21-40 ปี แบ่งออกเป็น 2 กลุ่ม แบบสุ่มให้ได้รับยาเลียนแบบที่ผลิตในประเทศไทย และยาต้นแบบที่ผลิตจากประเทศฮังการี ในการบริหารยาครั้งแรก คือ รับประทาน 1 เม็ด ประกอบด้วย 0.75 มิลลิกรัม ของฮอร์โมนลีโวนอร์เจสเตรล จากนั้นเว้นระยะอย่างน้อย 1 สัปดาห์ เพื่อการบริหารยาครั้งที่สอง โดยอาสาสมัครจะได้รับยาอีกชนิดหนึ่งสลับกับการบริหารยาครั้งแรก มีการเจาะเลือดหาระดับยาลีโวนอร์เจสเตรลในช่วงระยะต่าง ๆ โดยใช้วิธี radio-immunoassay และนำผลวิเคราะห์ระดับยามาหาค่าเภสัชจลนศาสตร์ของยาทั้งสอง สำหรับการวิเคราะห์ด้านชีวสมมูลของยาทั้งสอง ใช้วิธี two way analysis of variance (ANOVA) สำหรับการศึกษาเชิงทดลองแบบข้ามเชิงสุ่ม*

***ผลการศึกษา*** *: ค่าเฉลี่ย ($\overline{X} \pm SD$) ของ $C_{max}$ (ความเข้มข้นสูงสุด) ของยาเลียนแบบที่ผลิตในประเทศไทย เท่ากับ 1.18 $\pm$ 0.12 ng/ml และของยาต้นแบบที่ผลิตในประเทศฮังการี เท่ากับ 1.14 $\pm$ 0.10 ng/ml สำหรับค่า 90% confidence interval for the difference ค่าเฉลี่ยของ log $C_{max}$ คือ 99.54-120.78%*

*: ระยะเวลาที่ความเข้มข้นขึ้นสูงสุด ($T_{max}$) ของยาเลียนแบบที่ผลิตในประเทศไทย และยาต้นแบบที่ผลิตในประเทศฮังการี มีค่าเท่ากับ 1.56 $\pm$ 0.73 และ 1.58 $\pm$ 0.67 ชั่วโมง ตามลำดับ ค่าแตกต่างของเวลาที่ความเข้มข้นสูงสุด มีค่าเท่ากับ 1.27%*

*: ค่าเฉลี่ย ($\overline{X} \pm SD$) ของ $AUC_{0-\infty}$ (area under the curve) ของยาเลียนแบบที่ผลิตในประเทศไทย และยาต้นแบบที่ผลิตในประเทศฮังการี มีค่าเท่ากับ 2.14 $\pm$ 0.21 และ 2.09 $\pm$ 0.16 ng.h/ml ตามลำดับ และค่า 90% confidence interval for the difference ของค่าเฉลี่ยของ log $AUC_{0-\infty}$ คือ 103.27-121.89%*

*: หลักเกณฑ์ในการพิจารณาว่ายาเลียนแบบจะมีชีวสมมูลกับยาต้นแบบนั้น คือค่า 90% confidence interval for the difference ของค่าเฉลี่ยของ log $C_{max}$ และ log $AUC_{0-\infty}$ จะต้องอยู่ภายในช่วง 80-125%*

***สรุป*** *: ในการศึกษานี้ พบว่ายาเลียนแบบที่ผลิตขึ้นในประเทศไทยมีค่า 90% confidence interval for the difference ของค่าเฉลี่ยของทั้ง log $C_{max}$ และ log $AUC_{0-\infty}$ อยู่ในเกณฑ์ที่ยอมรับ จึงสรุปได้ว่ายาเลียนแบบที่ผลิตในประเทศไทย มีชีวสมมูลกับยาต้นแบบที่ผลิตจากประเทศฮังการี ซึ่งจะมีประสิทธิภาพในการรักษาไม่แตกต่างกัน*