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Study of bioequivalence of post coital contraceptions (Levonorgestrel 0.75 mg)

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Objective : *To determine whether a local product (BW_2) has equal efficacy to its innovator's product (Postinor®) by comparative the bioavailability of the two types of contraceptive tablets.*

Setting : *Department of Pharmacology, Department of Obstetrics and Gynaecology, Faculty of Medicine, Chulalongkorn University, Bangkok.*

Design : *Clinical Trial, Randomized crossover design.*

Material and Methods : *Twelve, healthy female volunteers aged 21- 40 years were randomly divided into two groups. Subjects in Group 1, by randomization took one tablet of a local product (BW_2) or the innovator's product. The drug free interval between the period was two weeks. The order of drug administration for subjects in Group II was reversed. The blood sample was obtained from antecubital according to schedule, and serum levonorgestrel concentration was analyzed by radio-immmunoassay. The pharmacokinetic analysis of serum levonorgestrel concentration from each treatment was established. The comparative bioavailability of the two products was determined by two-way analysis of variance (ANOVA) for a crossover design.*

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Result : *- The mean AUC (area under the curve) of local product (BW_2) and innovator's product (Postinor®) were 2.20 ± 0.13 and 2.15 ± 0.11 ng.h/ml, respectively. The 90 % confidence interval of difference of AUC mean (log transformed data) was 107.004 - 118.748 %*

- The mean C_{max} (peak serum concentration) for BW_2 was 1.23 ± 0.06 ng/ml and for Postinor was 1.16 ± 0.11 ng/ml. The 90 % confidence interval of difference of C_{max} mean (log-transformed data was 108.59 -126.53 %

The acceptance criteria for consideration of the bioequivalence of two products is when each 90 % confidence interval is within 80 -125 %.

Conclusion : *The study revealed that only 90 % confidence interval of difference of AUC mean was in the criteria of acceptance, but 90 % confidence interval difference of C_{max}, the upper limit was slightly higher than the criteria, so we could not conclude that the local product (BW_2) was bioequivalent to innovators's product (Postinor®)*

Keywords : *Postcoital contraception, Bioequivalence.*

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สุมนา ชมพูทวีป, สมัย ลีพิพัฒน์ไพบูลย์. การศึกษาชีวสมมูลของยาคุมกำเนิดหลังร่วมเพศ (Levonorgestrel 0.75 มิลลิกรัม). จุฬาลงกรณ์เวชสาร 2546 ก.พ;47(2): 87 – 95

วัตถุประสงค์ : *เพื่อศึกษายาสามัญเลียนแบบ (BW_2) มีประสิทธิภาพในการรักษาเท่ากับยาต้นแบบ (Postior®) โดยศึกษาเปรียบเทียบค่าทางเภสัชจลศาสตร์ของยาทั้งสองชนิด*

สถานที่ทำการศึกษา : *ภาควิชาเภสัชวิทยา และภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

รูปแบบของการศึกษา : *การศึกษาทางคลินิกเชิงทดลองแบบข้ามเชิงสุ่ม*

วัสดุและวิธีการ : *อาสาสมัครสตรี 12 คน อายุระหว่าง 21-40 ปี แบ่งออกเป็น 2 กลุ่ม แบบสุ่มให้ได้รับยาสามัญ (BW_2) และยาต้นแบบ (Postinor®) ในการบริหารยาครั้งแรกจากนั้นจะเว้นระยะ 2 สัปดาห์ เพื่อการบริหารยาครั้งที่สอง โดยอาสาสมัครจะได้รับยาอีกชนิดหนึ่งสลับกับการบริหารยาครั้งแรก มีการเจาะเลือดหาระดับยา Levonorgestrel ในช่วงระยะต่าง ๆ โดยใช้วิธี radio immunoassay และนำผลมาวิเคราะห์ระดับยามาเพื่อหาค่าเภสัชศาสตร์ของยาทั้งสอง สำหรับการวิเคราะห์ด้านชีวสมมูลของยาทั้งสอง ใช้วิธี two way analysis of variance (ANOVA) สำหรับการศึกษาเชิงทดลองแบบข้ามเชิงสุ่ม*

ผลการศึกษา : *ค่าเฉลี่ยของ AUC (area under the curve) ของยาสามัญเลียนแบบ (BW_2) และยาต้นแบบ (Postinor®) มีค่าเท่ากับ 2.20 ± 0.13 และ 2.15 ± 0.1 ng h/ml ตามลำดับ และค่า 90 % confidence interval of difference ของค่าเฉลี่ยของ AUC (log transformed data) คือ 107.004 – 118.748 %*

: ค่าเฉลี่ยของ C_{max} (ค่าความเข้มข้นสูงสุด) ของยาสามัญเลียนแบบ (BW_2) เท่า กับ 1.23 ± 0.06 ng/ml และของยาต้นแบบ (Postinor®) เท่ากับ 1.16 ± 0.11 ng/ml สำหรับค่า 90 % confidence interval of difference ของค่าเฉลี่ยของ C_{max} (log transformed data) คือ 108.59 -126.53 %

: การพิจารณาว่ายาทั้งสองจะมีชีวสมมูลกันหรือไม่นั้นมีหลักเกณฑ์ดังนี้คือค่า 90 % confidence interval for the difference ของค่าเฉลี่ย Cmax และ AUC_{∞} (log transformed data) จะต้องอยู่ภายใน 80 - 125 %

สรุป : *การศึกษาพบว่ายาสามัญเลียนแบบ (BW_2) มีค่า 90 % confidence interval of difference of AUC mean ที่อยู่ในเกณฑ์ แต่สำหรับค่า 90% confidence interval of difference of C_{max} นั้นพบว่าอยู่สูงกว่าเกณฑ์ จากผลดังกล่าวนี้ จึงสรุปได้ว่ายาสามัญเลียนแบบ (BW_2) นั้น ไม่มีชีวสมมูลกับยาต้นแบบ (Postinor®)*

In the beginning of the new millennium, the world population has more than 6 billions, there is high growth rate in developing countries. Thailand, one of the countries in South East Asia is successful in National Family Planning program, has the population growth rate less than 1.6 %.[1] There is a cafeteria of choice for Thai women to contraceptives, e.g. oral pills, IUD, injectable, implant, etc. While most contraceptives are appropriate for use before sexual intercourse. At present there are several methods of contraception that a women can use within a short time after unprotected intercourse often so-called "morning after pills" / "Post coital contraception". These regimens are better named emergency contraceptives. [2]

In Thailand, the levonorgestrel emergency contraceptive regimen is one of the effectiveness for the temporary contraception, that are increasing demand among Thai youth couples. This regimen is more popular than the "Yuzpe regimen".

The levonorgestrel regimen consists of 0.75 mg levonorgestrel taken in two doses of twelve hours apart and started within 48 hours after an unprotected intercourse. The mechanism for prevention of pregnancy is unclear. It is believed that this regimen has a high dose of progestin, it will increase the movement of the fallopian tubes, or it may change endometrium not suitable for fertilized ovum. Almost it does not inhibit ovulation. [3]

In a multicenter trial conducted by the World Health Organization, the observed failure rate per treated cycle for 0.75 mg dose was 0.8 %.[4] This rate is similar to that of other reports for emergency postcoital contraception. Bleeding and spotting are the most reported adverse events. Other side effects are headache, dizziness, and nausea. [5-10]

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 (BW_2, Thai Pharmaceutical Factory, Bangkok). The present paper described a comparative bioavailability of these two types of tablets. The objective was to determine whether the local product (BW_2) has equal efficacy to its innovator's product (Postinor ®).

Materials and Methods

Permission for the study was given by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University. Informed consent was obtained from each of the volunteers.

Twelve normal and healthy female volunteers, aged between 21-40 years, were randomly divided into two groups. All subjects had regular menstrual cycles (28 $\pm$ 7 days) and had not used any steroidal agents nor lactated for at least three months prior to the admission. No other drugs were taken during the course of the study. A medical history was taken from each subject before entering the study and a full medical and gynecological examinations, were performed. Normal liver and kidney functions were confirmed by routine laboratory tests.

This study was a single dose of the randomized crossover design. Twelve female volunteers were randomly divided into two groups. Subjects in Group I, took one tablet of innovator's product or local product according the assignment of treatment by randomization. The drug free interval between the period was two weeks. The order of drug administration was reversed for subjects in Group II.

Both the Innovator's product (Postinor®) and local product (BW_2,) tablets contained 0.75 mg levonorgestrel. The BW_2 were batched lot No AA and Postinor® were the batched lot No T 86264 Mfd. 06 1998.

Prior to the dosing events, the subjects had fasted overnight, starting from midnight of the previous day. At about 7-8 a.m., the drug was administered to subjects with 200 ml of tap water. A standardized lunch and snack were given to each subject after blood samplings were drawn at 4, and 8 hours, respectively.

From each woman, a blood sample was obtained from antecubital vein immediately before and at 1,1.5,2,2.5,3,3.5,4,6,10 and 24 hour after taking the tablet. Blood samples were allowed to clot at room temperature at least 30 minutes and then centrifuged. The separated serum was stored at -20°C until analyzed for levonorgestrel content by radioimmunoassay.[11] The intraday and inter-day precision were validated. The % coefficient of variation (c.v.) for intraday and inter-day were 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 graphing method. The peak serum concentration, c_{max} and the time to peak serum concentration, t_{max} were directly observed from the data. The area under the serum concentration-time curve, AUC was calculated using the linear trapezoidal rule and extended to infinite time.[12]

Statistical Analysis

Comparative bioavailability of the local product (BW_2) of 0.75 mg levonorgestrel tablet in the present study relative to its innovator's product (Postinor®) was assessed using the relevant pharmacokinetic parameters, c_{max} and AUC_{∞}. Both were transformed to logarithmic scale for statistical analysis.

The difference of the corresponding log c_{max} and log AUC_{∞} between the two products were determined by two-way analysis of variance (ANOVA) for a crossover design[13] at the significant level of α = 0.05.

The 90 % confidence interval (Two one–sided tests) for the differences of c_{max} and AUC_{∞} means based on log transformed data were calculated.[14,17]

Acceptance Criteria[12,15,16]

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

Results

Twelve female subjects, average mean age was 33.5 years, ranged 24-40 years. Their average weight and height were 52.7 kg and 158.6 cm, respectively. Their average Body Mass Index (BMI) was 21.1. All subjects had regular menstrual cycles. The results of their laboratory tests for liver and kidney functions were within normal limits.

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 eleven women after both products. Serum concentration in all subjects were slightly higher when taking BW_2 (Table 1, Table 2, Fig1).

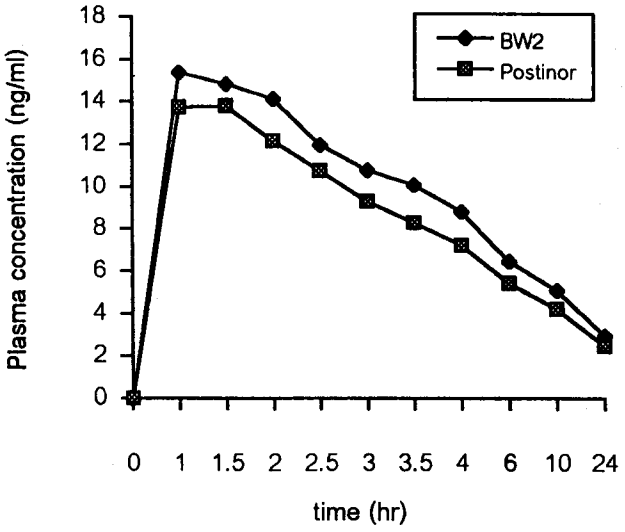

Figure 1. Mean serum levonorgestrel concentrationstime curve from12 subjects following oraladministration of 0.75 mg tablets of BW_2 and Postinor®

The pharmacokinetic parameters used for the evaluation of bioequivalence between BW_2 and Postinor® were the peak serum levonorgestrel concentration, c_{max}, the time to peak serum levonorgestrel concentration, t_{max}, and the area under the serum levonorgestrel concentration-time curve, AUC. The first two parameters (c_{max}, t_{max}) referred to rate of drug absorption; meanwhile the later (AUC) indicated the extent or amount of drug absorption into systemic circulation. All these parameters were derived from individual serum levonorgestrel concentration-time profile. Their mean values were summarized in Table 3.

Table 1. Serum levonorgestrel concentration (ng/ml) from 12 subjects following oral administration of 0.75 mg of tablets of BW_2 (Thai pill).

Subject	Time (hr)										
No.	0	1.0	1.5	2.0	2.5	3.0	3.5	4.0	6.0	10.0	24.0
1	0	9.00	14.07	16.04	11.79	8.55	7.69	7.38	4.81	3.82	1.92
2	0	15.22	9.09	6.79	7.54	5.08	4.60	4.01	2.94	1.68	1.43
3	0	10.72	13.38	12.60	10.76	11.40	7.45	4.54	3.96	3.10	1.53
4	0	21.67	21.78	21.77	19.92	16.33	15.94	14.24	12.21	10.97	6.37
5	0	16.78	14.11	11.93	9.80	8.38	7.74	7.52	4.63	3.75	1.90
6	0	12.11	16.53	14.50	10.88	12.81	14.10	10.66	8.33	6.87	3.72
7	0	14.98	17.68	16.48	15.30	14.24	13.31	11.52	10.80	5.46	3.78
8	0	15.05	10.30	11.76	10.67	11.46	16.03	13.87	8.40	7.66	4.05
9	0	12.45	14.43	14.85	11.64	9.32	9.52	8.56	4.93	5.23	2.11
10	0	18.03	14.47	15.88	13.36	11.87	9.43	9.15	7.66	4.41	3.18
11	0	20.10	16.76	15.95	12.04	10.55	8.60	7.61	4.83	4.90	3.47
12	0	18.31	15.43	10.93	9.96	9.45	6.70	6.66	4.00	3.33	1.92
$\bar{x}$	0	15.37	14.84	14.13	11.97	10.79	10.09	8.81	6.46	5.10	2.95
S.D.	0	3.83	3.31	3.71	3.15	2.96	3.80	3.26	2.96	2.47	1.44

Table 2. Serum levonorgestrel concentration (ng/ml) from 12 subjects following oral administration of 0.75 mg of tablets of Postinor®

Subject	Time (hr)										
No.	0	1.0	1.5	2.0	2.5	3.0	3.5	4.0	6.0	10.0	24.0
1	0	11.72	12.85	10.98	9.63	11.28	9.64	6.85	6.18	4.80	2.37
2	0	14.65	12.33	10.73	9.81	6.87	5.43	5.71	3.58	3.22	2.31
3	0	11.22	10.07	9.05	7.10	6.81	5.53	4.68	4.39	2.89	1.75
4	0	22.53	19.92	17.78	14.48	12.64	11.13	9.69	6.54	5.69	3.49
5	0	13.60	13.70	10.56	10.73	9.50	10.15	7.87	4.85	3.19	1.79
6	0	19.99	16.97	14.82	12.84	13.52	9.52	9.14	8.00	6.36	3.44
7	0	14.95	18.27	16.18	16.01	12.60	11.23	9.61	8.69	6.33	3.81
8	0	6.33	12.68	12.62	12.22	13.20	12.93	11.06	6.06	5.25	3.50
9	0	12.19	11.78	11.32	10.50	8.56	8.04	7.64	4.46	3.31	1.63
10	0	15.91	16.25	11.12	7.45	1.48	2.32	3.04	4.61	2.64	1.72
11	0	12.66	11.00	13.37	11.82	9.36	7.76	7.34	5.19	4.61	2.45
12	0	9.18	9.69	7.16	6.28	5.53	5.55	3.99	2.31	2.08	1.49
$\bar{X}$	0	13.74	13.79	12.14	10.74	9.28	8.27	7.22	5.41	4.20	2.48
S.D.	0	4.40	3.31	3.00	2.95	3.66	3.08	2.48	1.80	1.49	0.86

Table 3. Mean pharmacokinetic parameters ($\bar{X} \pm SD$) of levonorgestrel from 12 subjects following oral administration of 0.75 mg tablets of BW_2 and Postinor®

Parameters	Brands		90% Confidence Interval
	BW_2	Postinor®	of Mean Differences
AUC (ng.h/ml)	2.20 ± 0.13*	2.15 ± 0.11*	107.004– 118.748
C_{max} (ng/ml)	1.23 ± 0.06*	1.16 ± 0.11*	108.59 - 126.53
T_{max} (hr)	1.54 ± 0.72**	1.38 ± 0.57**	

N = 12 * Log transformed data ** Observed data

Discussion

Table 3 showed the mean pharmacokinetic parameters ($\bar{x} \pm SD$) levonorgestrel from 12 subjects following oral administration of 0.75 mg tablets of BW_2 and Postinor®. The mean AUC of BW_2 and Postinor® were 2.20 ± 0.13 and 2.15 ± 0.11 ng/ml, respectively. The 90% confidence interval of difference of AUC mean (log transformed data) was 107.004-118.748 %. This result was within 80 -125 % for criteria of acceptance.

The mean C_{max} for BW_2 was 1.23 + 0.06 ng/ml and for Postinor® was 1.16 + 0.11 ng/ml. The 90% confidence interval of difference of C_{max} mean (log transformed data) was 108.59-126.53 %. The upper bound was 126.53 % slightly higher for criteria of acceptance (>125 %). Probably, the C_{max} had very high variation.

The mean T_{max} for BW_2 and Postinor® were 1.54 ± 0.72 and 1.38 ± 0.57 hours, respectively. The difference of time of peak serum levenorgestrel concentration in this study was 11.59 % which was in criteria which it is not more than 20 %.

At present,[17] the two pharmacokinetic parameters, C_{max} and AUC are used to be considered for bioequivalence of two products. Each of 90 % confidence interval for difference of C_{max} and AUC means (log transformed data) should be within 80 - 125 %. This study revealed that only 90 % confidence interval of difference of AUC mean was in the criteria of acceptance, but 90% confidence interval of difference of C_{max}, the upper limit was slightly higher than the criteria. It may be that the product "BW_2" had a higher rate of drug absorption than the innovator's product (Postinor®). In conclusion, we could not conclude that the BW_2 was bioequivalent to Postinor®.

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