Chulalongkorn Medical Journal

Volume 31
Issue 5 *May 1987*

Article 5

5-1-1987

Pharmacokinetic/pharmacodynamic clinical trials ofCAPRONOR implants

Pramuan Virutamasen

Smai Leepipatpaiboon

Chatporn Ussanachitt

Supawat Chutivongse

นิพนธ์ต้นฉบับ

Pharmacokinetic/pharmacodynamic clinical trials of CAPRONOR® implants*

Pramuan Virutamasen** Smai Leepipatpaiboon**
Chatporn Ussanachitt** Supawat Chutivongse**

Virutamasen P, Leepipatpaiboon S, Ussanachitt C, Chutivongse S. Pharmacokinetic/pharmacodynamic clinical trials of CAPRONOR® implants. Chula Med J 1987 May ; 31 (5) : 377-385

The Pharmacokinetic/pharmacodynamic effects of Capronor® implants were studied in normal menstruating Thai women at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Capronor® implants of 2.5 cm long were inserted ; six subjects had single implants inserted while another group of six had two implants. A subsequent study was conducted on the single 4 cm devices in five subjects. Minimal temporary localized reactions were observed in both studies.

In the study of 2.5 cm devices, all subjects with one implant as well as two implants showed complete inhibition of ovulation as determined by serum progesterone. The levels of serum estradiol were significantly suppressed throughout the treatment cycle in 1 out of 6 subjects with one implant and 4 out of 6 subjects with two implants. The serum levonorgestrel levels varied between 180-780 pg/ml in 10 out of 12 subjects. In the study of 4 cm devices, beside the suppression of ovarian function in all subjects, the serum levonorgestrel levels between 340-900 pg/ml were observed in 4 out of 5 subjects. This preliminary study indicated that increasing the length of the devices from 2.5 cm to 4 cm induced an increase in the concentration of serum levonorgestrel up to a level sufficient to inhibit ovulation in a 28-day treatment period. However, further clinical studies of Capronor® implants for assessing contraceptive efficacy and side-effects on a large scale should be carried out.

Reprint requests : Virutamasen P. Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10500, Thailand.
Received for publications. May 15, 1986.

---

* Presented at the International Symposium on Recent Advances in Fertility Regulation, 29 April-2 May 1986, HANGZHOU, The People's Republic of China.

**Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University.

ประมวล วีรุตมเสน, สมัย ลีพิพัฒน์ไพบูลย์, ฉัตรพร อุษณาจิตต์, ศุภวัฒน์ ชุติวงศ์. เภสัชจลนศาสตร์/เภสัชพลศาสตร์ของยาคุมกำเนิดชนิดฝังใต้ผิวหนัง (Capronor). จุฬาลงกรณ์เวชสาร 2530 พฤษภาคม; 31 (5) : 377-385

ได้ทำการศึกษาเภสัชจลนศาสตร์ และเภสัชพลศาสตร์ของยาคุมกำเนิด Levonorgestrel ซึ่งบรรจุอยู่ในหลอดฝังใต้ผิวหนังกับสตรีไทยที่มีร่างกายสมบูรณ์และมีเลือดระดูเป็นปกติ ที่ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย แบ่งสตรีอาสาสมัครออกเป็น 3 กลุ่ม สตรีสองกลุ่มแรกกลุ่มละ 6 คน ฝังยาคุมกำเนิดใต้ผิวหนังที่ด้านในของแขนหรือข้อพับประมาณ 2 ซ.ม. 6 คนแรกฝังหลอดยาคุมกำเนิดขนาดยาว 2.5 ซ.ม. คนละ 1 อัน กลุ่มที่ 2 ฝัง 2 อัน ส่วนกลุ่มที่ 3 จำนวน 5 คนฝังหลอดยาคุมกำเนิดขนาดยาว 4 ซ.ม. คนละ 1 อัน สตรีทุกคนจะฝังยาคุมกำเนิดใต้ผิวหนังระหว่างวันที่ 1-5 ของรอบประจำเดือนและฝังอยู่นาน 4 สัปดาห์ ในขณะที่มียาฝังอยู่และหลังถอดยาฝังออก 6 สัปดาห์ จะเจาะเลือดสัปดาห์ละ 2 ครั้ง เพื่อหาระดับ levonorgestrel เอสโตรเจน โปรเจสเตอโรน และการเปลี่ยนแปลงทางชีวเคมีเป็นช่วง ๆ จากการศึกษาพบว่าระดับ levonorgestrel ในซีรั่มของสตรีกลุ่มที่ 1 และ 2 มีระดับสูง 150-780 พิโคกรัม/มล. ส่วนกลุ่มที่ 3 มีระดับสูง 340-900 พิโคกรัม/มล. และมีระดับสูงพอที่จะยับยั้งการตกไข่ของสตรีทั้ง 3 กลุ่ม ไม่พบการเปลี่ยนแปลงทางชีวเคมีในน้ำเหลือง

Beside being effective, safe and reversible, in developing countries the temporary contraceptives should not interfere with lactation, can be administered by non-physicians and are totally independent of coital activities. Long-acting steroidal contraceptives meet these requirements more satisfactorily than do the other methods currently in use. Thailand, as one of the developing countries, is no exception. The long-acting method in the form of injectable progestogen was introduced into the country in 1960, and now about 12-16 percent of all contraceptive acceptors use the injectable form.

In order to eliminate the initial extremely high peaks of progesterone in the blood resulting from the exponential (first-order) release characteristics of these injectables and to lower the overall body burden of the steroid, in the early 1970 researchers had been looking for implantable delivery systems which were expected to release drug at a constant rate (zero-order). In addition to the reduction of the metabolic demand on the liver, it was postulated that zero-order release may be less disruptive to end-organ function. It should minimize the bleeding irregularities which are the most common side-effects that cause injectable contraceptive discontinuation.

Norplant^{r} was the first implantable delivery system that has been placed on large scale clinical trials. The successful testing of Norplant^{r} in terms of efficacy as well as acceptability convinced the health policy makers in Thailand to include it as another method in the national family planning program in 1986. However, Norplant^{r} has two drawbacks. Firstly, the silicone rubber is non-biodegradable so a surgical procedure is required to remove the device. Secondly, due to the low permeability of levonorgestrel through silicone rubber, a large surface area is needed to achieve sufficient drug release, necessitating the use of multiple devices. In order to obviate the above-mentioned problems, the Contraceptive Development Branch of the United States National Institutes of Health (NIH) initiated a research program in 1973 to develop biodegradable drug-delivery system. The Research Triangle Institute in North Carolina, US, with support from the NIH, has developed a tubular implant with a wall of poly ε-caprolactone. Within which levonorgestrel is suspended in ethyl oleate.[1] After the drug supply is exhausted, the polymeric breakdown will yield ε-hydroxy caproic acid, which is further metabolized to carbon dioxide and water. The levonorgestrel in its current configuration is released to the body at an initial rate of 20 ug/cm/day and has a duration of action of more than one year.[2]

With the full support from the Task Force on Long-Acting Agents for Fertility Regulation of the WHO Special Programme for Research, Development and Research Training in Human Reproduction, the Capronor^{r} implants have been studied for their pharmacokinetic and pharmacodynamic effects in two stages. In the first stage, the original design of 2.5 cm long device was chosen to be followed in the second stage by the 4 cm long device.

Materials and Methods

1. Subject selection

The following criteria were used for subject selection :

a. Healthy, informed female volunteers
b. Aged between 18-35 years and not in postmenopausal condition.
c. Throughout the study, only barrier methods of contraception will be allowed.
d. Not presently lactating or have stopped lactating at least 70 days prior to the study.
e. Have been menstruating regularly (cycle length 24-35 days) during the past 6 months, or at least 70 days postpartum or postabortion, and have had one normal cycle (2 normal bleeding episodes) since delivery or abortion cycles for 6 months prior to pregnancy.

In the first stage with the 2.5 cm long devices, a group of 6 subjects were each implanted with one rod, and another group of 6 with two rods. Later in the second stage, the single 4 cm long devices were implanted in 5 subjects. The characteristic profiles of all volunteers are shown in Figure 1. The same volunteers were used in the second stage.

Categories	No. of CAPRONOR^r	
	One implant (N-6)	Two implants (N-6)
1. Age (years)	22 - 35 (28.7 ± 5.8)	23 - 35 (33.0 ± 2.0)
2. No. of living children	0 - 2 (1.3 ± 0.8)	1 - 5 (3.0 ± 1.4)
3. Body weight (kg)	58 - 68 (63.3 ± 4.1)	45 - 60 (54.2 ± 6.9)
4. Weight/Height^2 (kg/m^2)	22.9 - 29.4 (26.3 ± 3.1)	18.9 - 26.7 (23.3 ± 3.2)
5. Blood pressure (mm Hg)	100/60 - 120/70 (180.3 ± 7.5/65.0 ± 5.5)	90/60 - 130/90 (106.7 ± 16.3/70.0 ± 11.0)

Figure 1 The characteristic profiles of volunteers

2. Insertion and removal technique

The devices of 0.24 cm in diameter and either 2.5 cm or 4 cm in length were inserted subcutaneously at the medial aspect of the upper arm using a standardized insertion and removal procedure[3].

3. Study design

Blood samples were taken twice weekly for determination of estradiol and progesterone to confirm the ovulation during the control cycle. The devices were inserted during the first five days of the subsequent cycle and were left in situ for 28 days. The insertion site was examined twice weekly During the treatment and the follow-up cycles blood was taken twice weekly for estimation of estradiol, progesterone and levonorgestrel. The routine haematological analysis and biochemical parameters of the liver function test were also determined during the control, treatment and follow-up cycles in the first stage. Menstrual diary cards were exactly recorded.

Results

1. Insertion and removal of devices

The procedure was easily accomplished and it was well tolerated by the subjects. Local irritation was minimal.

2. Hematological analysis and biochemical parameters of the liver function test.

The results are shown in Figure 2. There were no siginificant changes in hematological analysis during the control, treatment and follow-up cycles whether with one or two rods. Minimal changes were observed in total and indirect bilirubin in the treatment and the follow-up cycles among the one implant group, but they were still within normal limits. As no significant changes in the hematological analysis and biochemical parameters of the liver function test were observed during the first stage of study, all these laboratory procedures were then omitted in the second phase of study.

Laboratory test	Mean ± S.D.					
	One implant			Two implants		
	Control	Treatment	Follow-up	Control	Treatment	Follow-up
Hematological analysis						
Hemoglobin (gm%)	12.6 ± 1.7	12.4 ± 1.0	12.6 ± 1.1	12.6 ± 1.1	13.1 ± 0.7	12.6 ± 1.3
Hematocrit (vol %)	41.1 ± 4.6	41.4 ± 3.3	41.4 ± 3.7	40.8 ± 3.1	42.6 ± 1.9	41.2 ± 3.1
Biochemisty analysis						
Total bilirubin (mg%)	0.4 ± 0.2	0.6 ±0.2**	0.5 ± 0.2*	0.4 ± 0.1	0.5 ± 0.2	0.4 ± 0.1
Indirect bilirubin (mg%)	0.2 ± 0.1	0.4 ± 0.2	0.4 ±0.1**	0.2 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
Total protein (gm%)	7.6 ± 0.3	7.4 ± 0.6	7.5 ± 0.1	7.8 ± 0.2	7.8 ± 0.4	7.5 ± 0.3

Blood urea nitrogen (mg%)	10.5 ± 2.0	9.4 ± 2.0	9.5 ± 1.3	10.5 ± 4.1	10.9 ± 1.7	11.2 ± 2.9
Creatinine (mg%)	1.0 ± 0.2	1.1 ± 0.6	0.8 ± 0.1	1.1 ± 0.5	0.8 ± 0.1	0.8 ± 0.1
SGOT (mIU/ml)	13.8 ± 6.2	10.0 ± 2.1	13.2 ± 3.8	15.3 ± 8.8	10.0 ± 2.0	10.9 ± 2.5
SGPT (mIU/ml)	7.2 ± 5.4	4.9 ± 1.5	8.1 ± 5.3	8.0 ± 6.1	5.4 ± 2.4	6.4 ± 2.8
Alkaline phosphatase (mIU/ml)	19.6 ± 4.4	17.6 ± 3.1	23.2 ± 13.8	18.9 ± 8.1	19.9 ± 7.9	18.0 ± 6.6

Figure 2 Mean and standard deviation with significant levels of hematological analysis and biochemistry analysis of liver function test from paired "t" tests

3. Bleeding pattern

The results of the first stage are shown in Figure 3. During the treatment cycle of the dual implants group, the bleeding days were statistically significant increase With the 4 cm devices, the bleeding pattern was more different during the follow-up cycles as shown in Figure 4.

Bleeding patterns	Mean ± S.D.					
	One implant			Two implants		
	Control	Treatment	Follow-up	Control	Treatment	Follow-up
Cycle length (days)	27.0 ± 1.7	31.8 ± 12.7	26.6 ± 8.0	27.3 ± 3.1	31.5 ± 13.0	31.4 ± 5.4
Bleeding episode (time)	1.0 ± 0.0	1.2 ± 0.4	1.0 ± 0.0	1.0 ± 0.0	1.2 ± 0.4	1.0 ± 0.0
Bleeding run (days)	3.8 ± 1.0	5.3 ± 3.0	3.8 ± 1.0	3.8 ± 1.0	6.8 ± 4.0*	3.8 ± 0.5
: Spotting (days)	1.2 ± 1.2	2.9 ± 3.1	0.5 ± 0.6	0.3 ± 0.5	4.5 ± 3.7*	0.8 ± 0.5
: Bleeding (days)	2.7 ± 0.5	2.4 ± 0.9	3.2 ± 0.5	3.5 ± 1.0	2.3 ± 1.6	3.0 ± 0.0

Figure 3 Bleeding patterns of the 2.5 cm devices.

Bleeding patterns	Mean ± S.D.		
	Control	Treatment	Follow-up
Cycle length (days)	27.1 ± 1.9	36.0 ± 9.92	34.40 ± 11.34
Bleeding episode (time)	1.0 ± 0.0	0.40 ± 0.54	1.6 ± 0.89
Bleeding run (days)	3.8 ± 1.0	3.0 ± 2.47	10.0 ± 2.54*
: Spotting (days)	1.1 ± 0.6	1.6 ± 2.3	4.0 ± 1.58*
: Bleeding (days)	2.9 ± 0.6	1.2 ± 2.68	6.2 ± 3.7*

Figure 4 Bleeding patterns of the 4 cm devices.

4. Ovarian function

All subjects with one or two implants of 2.5 cm devices as well as with one implant of 4 cm devices showed complete suppression of serum progesterone levels throughout the treatment cycle. There was also a significant suppression of estradiol levels throughout the treatment cycle in 1 out of 6 subjects with one implant of 2.5 cm devices, and 4 out of 6 subjects with two implants. With the 4 cm devices, 4 out of 5 subjects showed the suppression of estradiol levels. It was suggested that the effect of the drug on follicular function was dose-related.

5. Levonorgestrel levels

Figures 5 to 9 show the levels of levonorgestrel from this study. With the single 2.5 cm devices, the levonorgestrel levels (pg/ml) throughout the treatment cycle varied among the 6 subjects. Levels between 180-320 pg/ml were observed in 3 out of 6 subjects. One subject had levels rising to a range of 630-780 pg/ml while the remaining two showed levels between 40-180 pg/ml. With with implants, the levels were higher than with one implant at an average range of between 200-650 pg/ml. Using the 4 cm devices, levels of levonorgestrel between 340-900 pg/ml were observed in 4 out of 5 subjects.

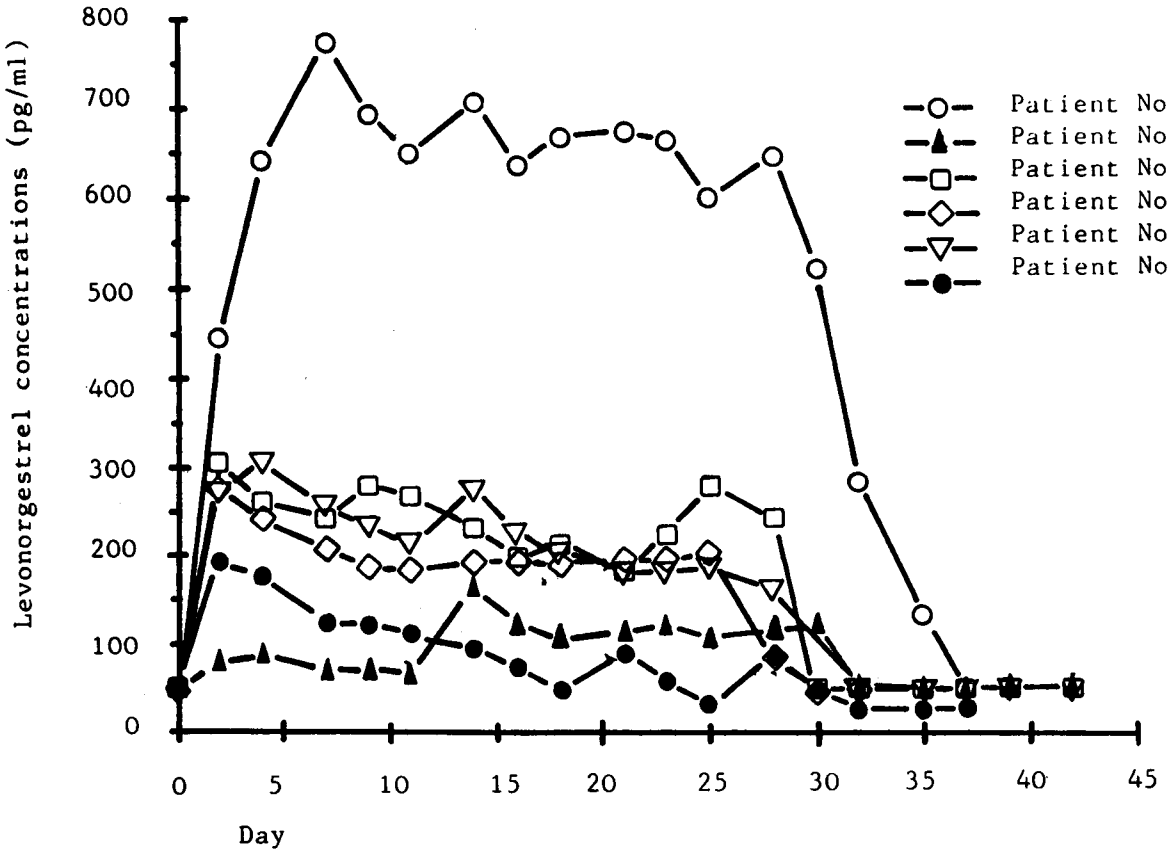

Figure 5 Levonorgestrel levels of the single 2.5 cm devices

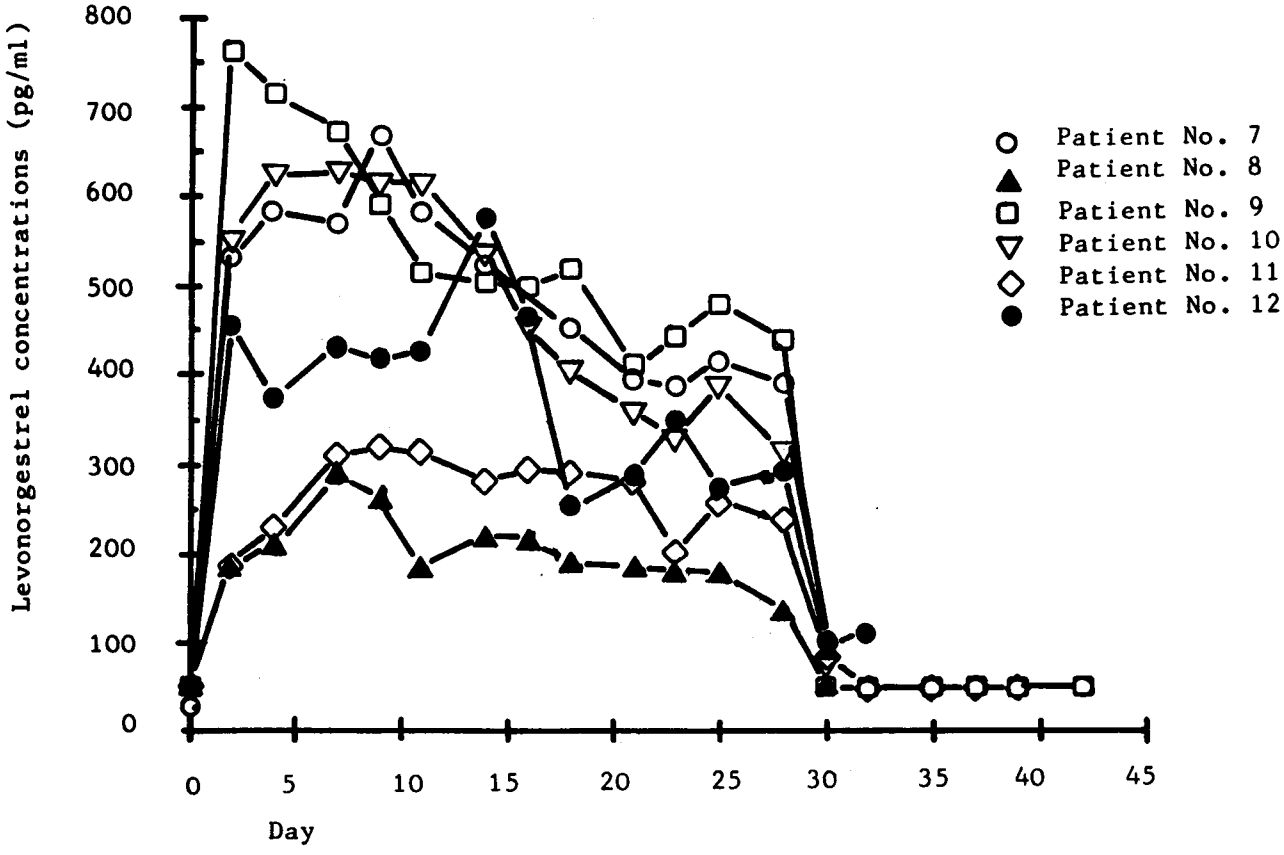

Figure 6 Levonorgestrel levels of the double 2.5 cm devices

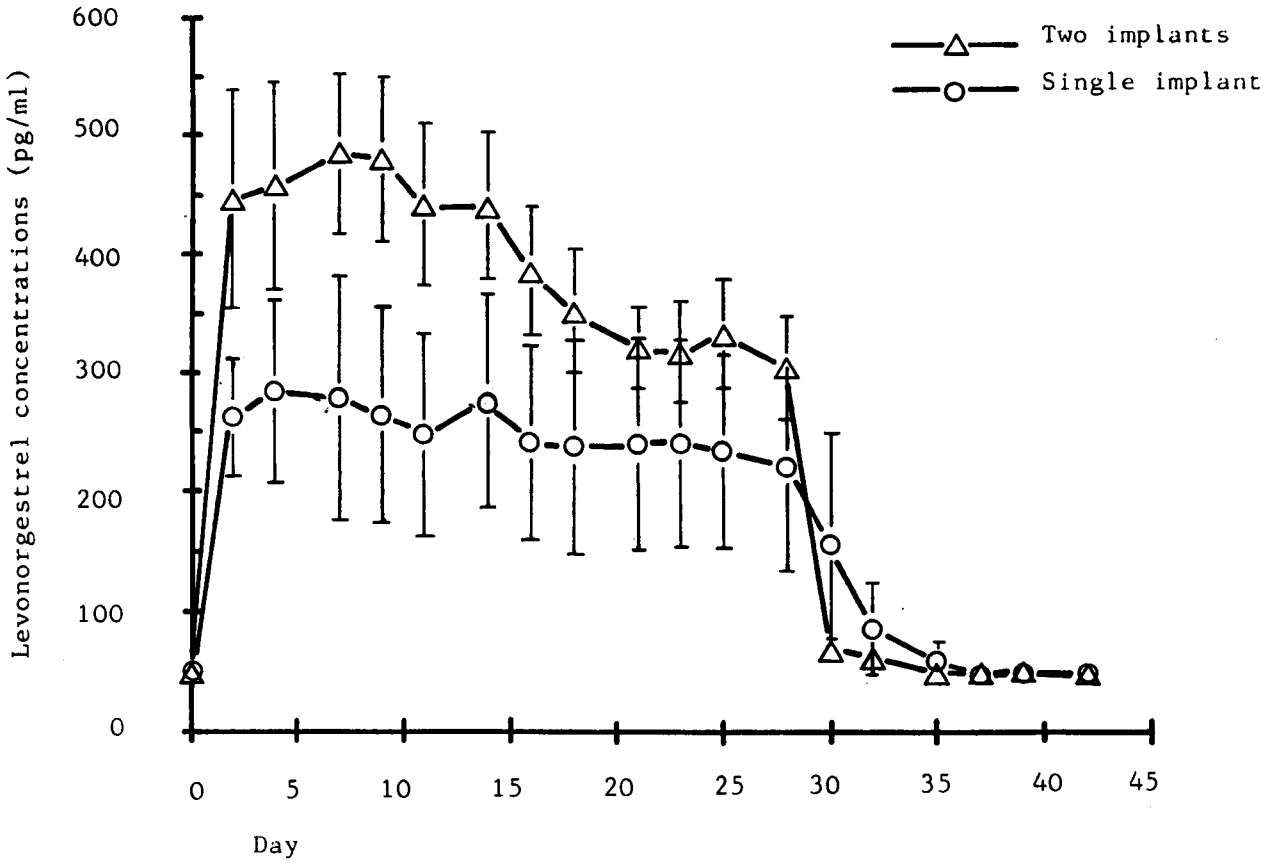

Figure 7 Levonorgestrel levels of the 2.5 cm devices

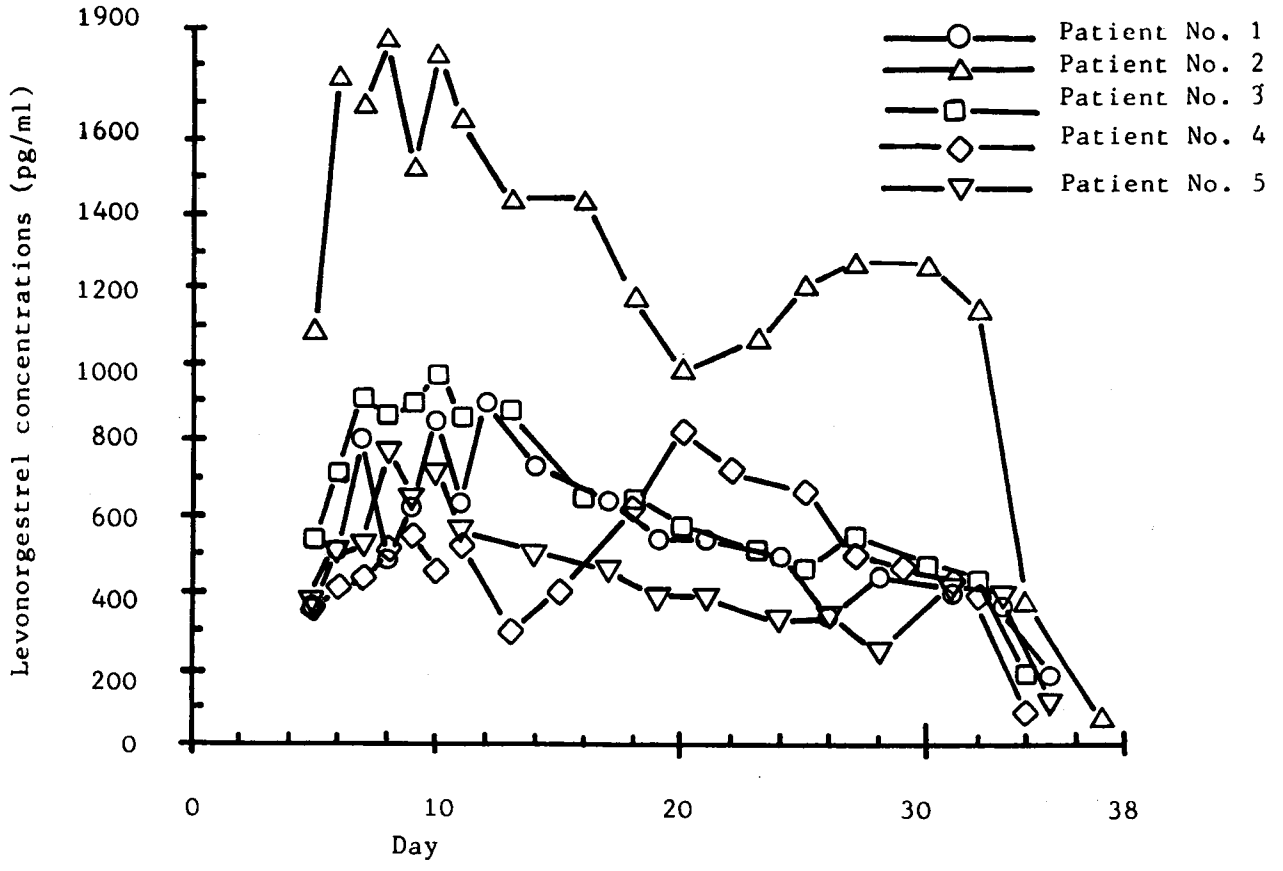

Figure 8 Levonorgestrel levels of the 4 cm devices

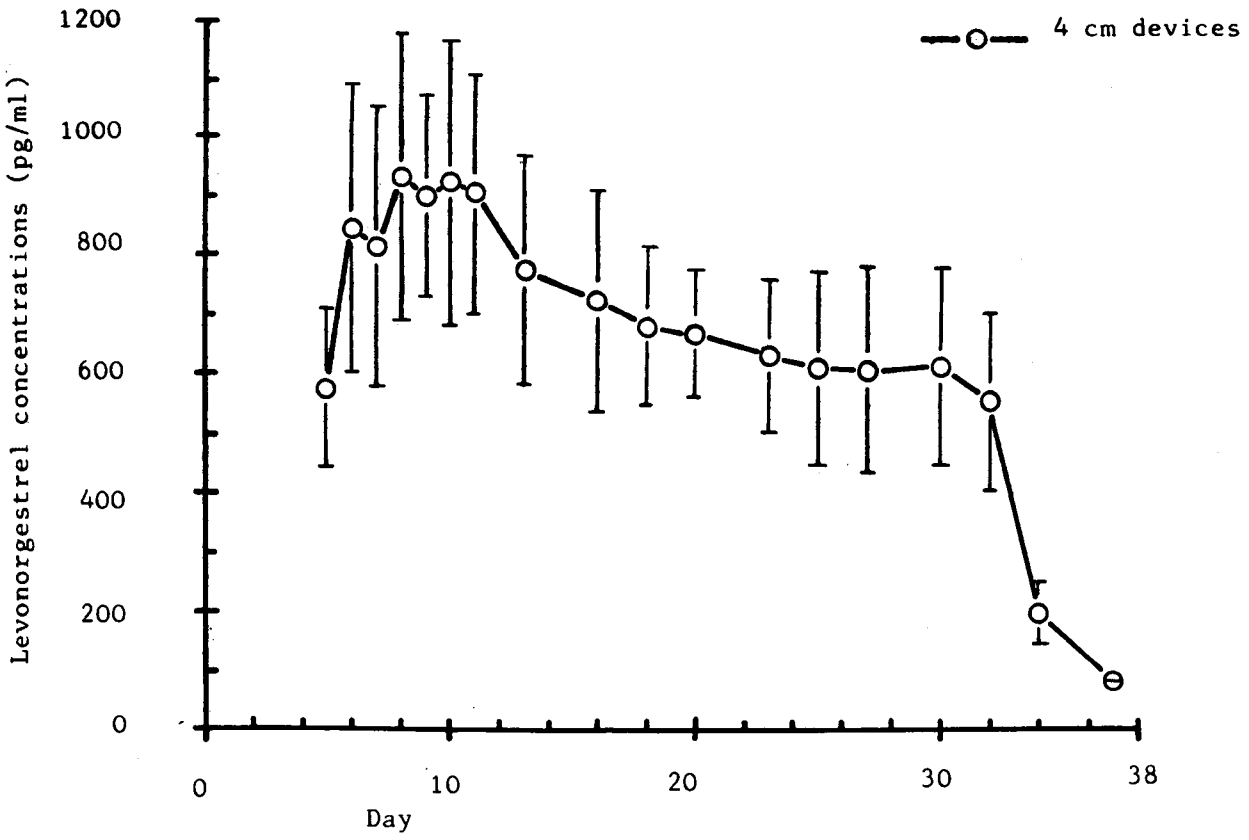

Figure 9 Adjusted values of the 4 cm devices

Discussion

The study of Capronor[r] implants appeared to be quite satisfactory for two reasons, regardless of the number or the length of the devices.

1. The medial aspect of the upper arm seemed to be an appropriate site for insertion because it showed rapid absorption with effective levels of levonorgestrel. All subjects tolerated the devices very well with minimal local reactions.

2. The controlled releasing rate of levonorgestrel was rather constant throughout the treatment cycle, which has been one of the prime objectives in the development of the implantable delivery system.

Some fluctuations in serum levonorgestrel levels observed from sample to sample in each subject may be in part due to the differences in SHBG levels and the clearance rates[4]. Bleeding irregularities were also found and seemed to be more frequent in the subjects using the 4 cm devices. These events were not unexpected side-effects as they could be seen with other forms of progestogen-only contraceptives, but were in contradiction to the other study[5] in which no intermenstrual bleeding was observed with the single Capronor[r] implants. This study gives an indication that increasing the length of the devices from 2.5 cm to 4 cm induced an increase in the concentration of serum levonorgestrel up to a level sufficient to inhibit ovulation in a single treatment cycle.

In summary, the levonorgestrel Capronor[r] implantable delivery system provides a promising, single-implant and potentially biodegradable approach to fertility regulation. The single implant of 4 cm long devices should be further studied on a large scale for assessing the contraceptive efficacy and side-effects.

Acknowledgements

This investigation received financial support from the Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization. The authors are grateful to Mr. P.E. Hall for his assistance in the preparation of this manuscript.

อ้างอิง

1. Pitt CG, Gratzl MM, Jeffcoat RA, Schindler A. Zweidinger R. Sustained drug delivery systems. II. Factors affecting rates of release from poly (epsilon-caprolactone) and related biodegradable polyesters. J Pharm Sci 1979 Dec ; 68 (12) : 1534-1538
2. Pitt CG, Schindler A. Capronor-A biodegradable delivery system for levonorgestrel. In : Zatuchni GI, Goldsmith A, Schelton JD, Sciarra JJ, eds. Long-Acting Contraceptive Delivery Systems. Philadelphia : Harper & Row Publishers,1984. 48-63
3. Koetsawang S, Varakamin S, Satayapan S, Dusitsin N. Norplant[r] clinical study in Thailand. In : Zatuchni GI, Goldsmith A, Shelton JD, Sciarra JJ, eds. Long-Acting Contraceptive Delivery Systems. Philadelphia : Harper & Row Publishers, 1984. 459-470
4. Cekan SZ, Jia M, Landgren BM, Diczfalusy E. The interaction between sex hormone binding globulin and levonorgestrel released from vaginal rings in women. Contraception 1985 Apr ; 31 (4) : 431-439
5. Ory SJ, Hammond CB, Yancy SG, Hendren RW, Pitt CG. The effect of a biodegradable contraceptive capsule (Capronor[r]) containing levonorgestrel on gonadotropin, estrogen and progesterone levels. Am J Obstet Gynecol 1983 Mar 1 ; 145 (5) : 600-605