Research Report

Levonorgestrel Concentration in a Single Rod Implant Users for Six Months

Kadar Levonorgestrel Pemakai Susuk Keluarga Berencana Satu Batang selama Enam Bulan

Eka R. Gunardi[1], Biran Affandi[1], Flourisa Juliaan[2]

[1]Division of Reproductive Health
Department of Obstetrics and Gynecology
Medical Faculty of Indonesia University/
Dr. Cipto Mangunkusumo Hospital
[2]Family Planning Research and Development Center of BKKBN
Jakarta

Abstract

Objective: This research was conducted to measure levonorgestrel serum concentration Monoplant® after six months of usage.

Method: Thirty healthy women, 20 - 40 years old, and after been proven for fertility, had implants on their body. Levonorgestrel serum levels were measured monthly from the first month to the sixth month.

Result: Levonorgestrel serum concentration was still above 200 pg/ml until the sixth month. First month and second month serum concentration was not recorded while data for the following months were 338.9 pg/ml, 424.8 pg/ml, 320.3 pg/ml, and 337.5 pg/ml.

Conclusion: Levonorgestrel serum concentration in Monoplant® users was still above contraceptive level until six months.

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Keywords: single rod implant Monoplant®, levonorgestrel serum concentration

Abstrak

***Tujuan**: Penelitian ini dilakukan untuk mengetahui kadar levonorgestrel susuk satu batang Monoplant® sampai 6 bulan pemakaian.*

***Metode**: Sebanyak 30 orang perempuan sehat, berusia 20 - 40 tahun, dan telah terbukti fertilitasnya, dilakukan pemasangan susuk. Selanjutnya dilakukan pemeriksaan serum levonorgestrel setiap bulan sampai bulan keenam.*

***Hasil**: Kadar serum levonorgestrel hingga bulan keenam setelah pemasangan susuk tetap di atas 200 pg/ml. Kadar pada bulan pertama dan bulan kedua tidak ada data, kadar pada bulan-bulan selanjutnya adalah 338,9 pg/ml; 424,8 pg/ml; 320,3 pg/ml; dan 337,5 pg/ml.*

***Kesimpulan**: Kadar levonorgestrel pemakai susuk Monoplant® hingga bulan keenam masih di atas kadar kontrasepsi.*

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***Kata kunci**: susuk satu batang Monoplant®, kadar levonorgestrel*

Correspondence: Eka R. Gunardi. Department of Obstetrics and Gynecology, Dr. Cipto Mangunkusumo Hospital, Jakarta.
Telephone: 0816-399901, Email: eka_dhikita@yahoo.co.id

INTRODUCTION

Implant is one mean of contraception devices that is placed under the skin. Implants contain steroid hormones and can be used for 1 - 5 years; one of them is levonorgestrel (LNG) implant.[1,2]

Norplant®, as first generation of LNG implant, consisting 6 capsules, has been proven to be an effective long-term contraception for 25 years.[3-6] On later development[7-10], the implant number has been reduced to two rods and called Norplant2®, which later renewed to Jadena® (in Indonesia) or Jadelle® (in America).[11,12]

As the biggest acceptor of family planning country in the world, Indonesia has developed its own implant contraception which contains two LNG rods and called Indoplant®.[13,14] One LNG implant (Monoplant®) is hoped to be the best/most chosen for its practicality (to insert and to remove), and also for its effectiveness and safety for at least three years.

GENERAL DESCRIPTION FOR LEVONORGESTREL IMPLANT

Drug Release System of Implants

In the last three decades, a lot of research have been developed to determine the release control system of drugs, usually to determine the effective concentration of drugs pharmacologically. Drugs release control system technology is really developing, especially for oral and trans-dermal drugs or long-term drugs injected to the body, there is an issue of body rejection (bio-compatibility), and especially tissue rejection (tissue compatibility). The bio-compatibility reaction usually comes in toxic, carcinogenic, immunogenic, and inflammatory reactions.[15] This biocompatibility is related to the implant material (bio-material) that's been used.[16] Silicone, not only co-polymer dimethylsiloxane, but also methylvinylsiloxane, which has been used since 1950, is the most compatible biomaterial.

Silastic cylinder (medical grade polydimethylsiloxane) has been used on humans as implants and for other surgical means. This tube also has been placed permanently inside the body since 1950. As example, more than 200.00 hydrocephalus patients have used this cylinder as cerebrospinal fluid drainage for the rest of their lives without serious reaction to foreign bodies. Also, medical glue (silicone type A) has been long and massively used in surgery.

After implant is placed under the skin, there will be tissue rejection reaction ,which is induced by tissue damage that happens soon on insertion. Local inflammatory responses happen in sequelae of reactions: neutrophil, polymorphonuclear, eosinophil, and macrophage rejection. Later, tissue repair happens and granulation tissue is formed. Macrophages do not phagotize silastic cylinder, perivascular fibroblasts will tend to isolate this cylinder around with shelter or capsules of connective tissue. The formation of fiber-capsule around the tube is not easy to be moved and hard to pull when removing the implant.[15]

Since Folkman and Long (1964) found that silastic cylinder can be used to distribute drugs because of its sustain-release feature; also Dziuk and Cook, in vitro, proved drugs that came out from silastic cylinder were always in constant concentration; then Segal and Croxatto (1966) tried to use silastic cylinder that was planted beneath the skin as a system to distribute steroid hormones. This research became the foundation and concept to develop long-term contraception which we know as implant.[17-19]

First implant generation, Norplant®, consists of six capsules containing LNG on silicone elastomer matrix. After plantation, Norplant® soon releases 50 - 80 mcg LNG per day. On the first year of use, 40 - 50 mcg/day of LNG will be released. This number gradually decreases to 25 - 30 mcg/days on the fifth year of usage. Despite this reduction, Norplant® has been proved to successfully prevent pregnancy for seven years, with pregnancy number cumulatively on seventh year is 1%.[20,21]

Later, second generation implant was developed, Jadelle®, consisting only two rods. Because it uses new elastomer technology with lower silicone concentration, the rod becomes more flexible and soft, and drug release capability increases. Thus, 2 rods of Jadelle® have the ability to release LNG as effective as six capsules of Norplant®. Jadelle® on the first month releases LNG in about 100 mcg/days then decreases to 40 mcg/day until the 12th month and constantly releases 30 mcg/day on the 24th month. Jadelle® has been approved to be used for five years with cumulative pregnancy number in the fifth years is 1 %.[22]

Levonorgestrel Profile on Implant

Active hormone inside Norplant® and Jadena® is levonorgestrel or LNG, with a chemical name of dextrorotatory isomer - 13ß-ethyl-17α-ethinyl-17ß-hydroxy,18,19-dinorpregn-4-en-20-yn-3-one, which is a chemical derivative of 19-nortestosterone. LNG is a steroid hormone, with a strong progesterone activity and weak androgen activity, without estrogen. Chemical structure from LNG can be viewed on Figure 1.[23,24]

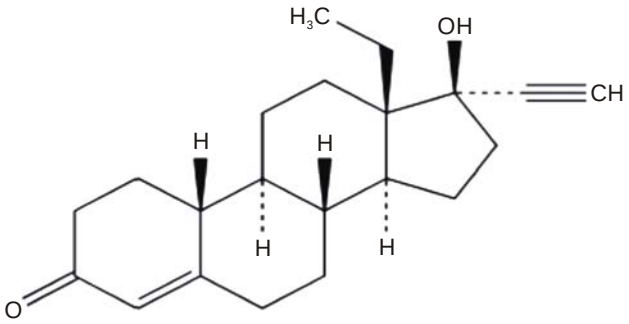

Figure 1. Levonorgestrel Chemical Structure ($C_{21}H_{28}O_2$)

Norgestrel consists of two stereoisomers: dextronorgestrel and levonorgestrel, only LNG is biologically active. LNG does not need bio-activation on the liver to work because LNG itself is an active metabolite. LNG bio-availability is almost 100%.[24-26]

Toxicology

Implant contraception system consists of two basic components: progestin as bioactive, and polymer or silastic or silicone elastomer as the mixing components. Thus, researches on implant toxicology are also designed to evaluate the progestin and polymer used.[27]

Research of LNG toxicology is completely done. Data about genotoxicity, carcinogenicity, effect on fetus growth, and effect on reproduction, in animals and humans, shows no toxicity as LNG given orally or in injection.[27]

Also toxicology research for polymer or silicone elastomer, which is used on Norplant® and Jadelle®, has proven its safety to be used along with the implant. This research is done on human and animal.[27-29]

Pharmacokinetic

Absorbtion

LNG serum concentration on average after Jadena® is implanted is 437 pg/ml, while Norplant-2® stays at 425 pg/ml (Figure 2). Average concentration for both implants are still above 300 pg/ml in a year. On the

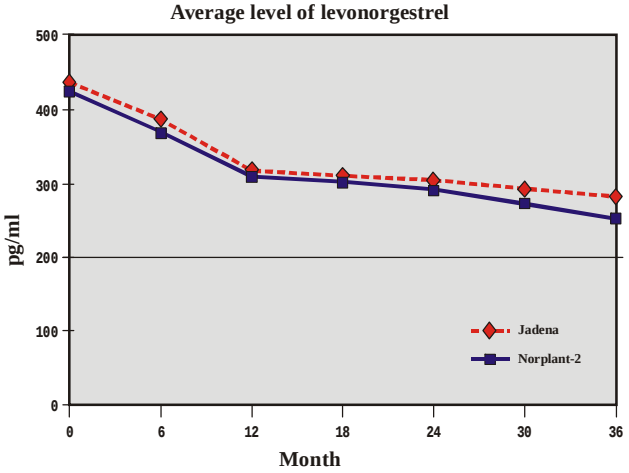

Figure 2. LNG Serum Concentration[32]

second and third year, LNG concentration is higher in women using Jadena® than in women using Norplant-2®. Although at the end of third year, LNG concentration in women using Jadena® becomes 275 pg/ml, this value is still 20% higher than Norplant-2® and is still above limit value to prevent pregnancy (200 mcg/ml).[44] LNG concentration in serum is influenced by body weight, SHBG level, and its metabolite clearance.[17,24-26,30,31]

Distribution and Excretion

After implanted, Norplant® releases 50 - 80 mcg of LNG daily. Few months after Norplant® implantation, LNG serum concentration is stable at 400 pg/ml. After five years of usage, it becomes 200 pg/ml. LNG release level of Jadena® is about 100 mcg/day on first month. Later, it declines to 40 mcg/day until 12 months and stays in 30 mcg/days at the 24th month. Serum concentration of 772 pg/ml is achieved in two days after implantation. Serum level after one, six, and three years are 437, 371, and 270 pg/ml, respectively.[33]

LNG mostly (> 90%) stays in blood and is bound to Sex Hormone Binding Globulin (SHBG) and albumin, only free LNG is biologically active.[26,31] There is a strong correlation between LNG concentration and SHBG. Level of SHBG will decrease following elevation of LNG concentration. Afterwards, SHBG will still be low following the reduction of LNG level.[17]

Most of LNG (40 - 68%) is excreted through urine, and 16 - 48% through feces. Soon after removing Norplant® outside the body, concentration of LNG will be decreased to less than 100 pg/ml and in 5 - 14 days, the concentration cannot be measured anymore.[17,32,34]

RESEARCH AND DEVELOPMENT MONOPLANT® IMPLANT

Monoplant® only contains progestin hormone, levonorgestrel. This implant consists of one flexible rod and inside, it contains same mixture amount as LNG with elastomer silicone. Implant rod is covered with thin-walled silicone (same with the one used on Jadelle® or Jadena®), and each pole is covered with Silastic (polydimethyl-siloxane) Medical Grade Adhesive. Every implant stick is 43 - 44 mm length and 2,5 - 2,6 mm in diameter, and containing 160 mg LNG as shown in Figure 3.[33,35]

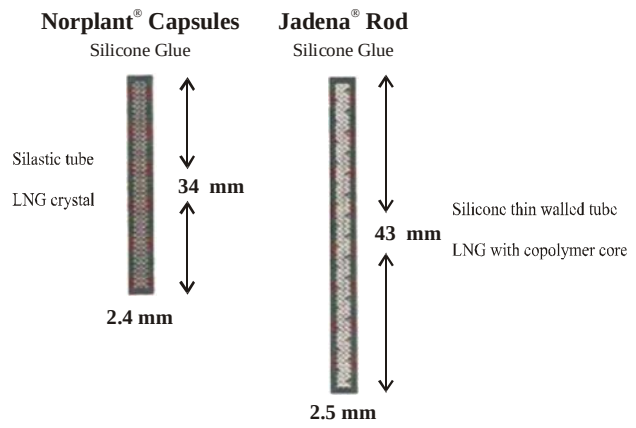

Figure 3. Norplant® capsules and Jadena® rod (and Monoplant®)

Substance used to make Monoplant® is not a new drug. LNG has been used for more than 30 years for contraception pills (combination pill and minipill) and implant.[35]

Monoplant® is predicted to be effective as contraception for three years. Because this *ALKON* is produced in Indonesia, advantages that will be gained are single implantation for three years, no need for routine control, cheaper so relatively affordable, and available in most health services. Monoplant® is a single rod, its insertion and removal are easier compared than any other implant.

METHOD

This research is a second phase Clinical Trial with pre and post design. It was held in Jakarta for six months with women subjects aged 20 - 40 years who still want to have next pregnancy.

Considering that this research was clinical trial phase two (done for the first time on patient), which was directed to evaluate whether drugs give therapeutic effect, sample size in this research was limited to 10 - 20 subjects[36] or 20 - 100 subjects.[37] Using numeric sample formula extraction for two paired groups, sample requirement was 22 subjects. In this research, it was agreed to use 30 subjects (recommendation from Research Ethics FMUI was 10 patients).

If the subjects had met all the requirement (inclusion and exclusion) and had been willing to sign informed consent, then the subject would have been categorized to research subject candidate. Later, research questionaire should be filled, and in four weeks before insertion, physical examination and laboratorium screening would be done.

After research subjects meet criteria mentioned above, Monoplant® could be inserted on menstruation period (day 1 to day 7). Subjects then would be followed for six months, revisitation would be done in the 4th week each month. On those periods, beside physical examination and side-effect evaluation, LNG, estrogen (E), and progesteron (P) examination were also done. Another biochemical examinations were triglyceride, total cholesterol, High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL), and also random blood glucose. Endometrium thickness and cervix discharge were also measured.

RESULTS and DISCUSSION

Research was conducted in Klinik Raden Saleh, Jakarta, and held between 2009 and 2010, as long as 6 months. Research subjects were women 20 - 40 years old who fulfilled inclusion criteria, and still wanted pregnancy after implant was removed from them.

As many as 30 family planning acceptors had approved to be chosen as subjects and follow this Monoplant® implant research. All subjects finished this research on schedule, six months. No subjects re-

quested to have their implants removed before research is over. Even, if allowed, they were all willing to use it untill the third year.

Subject Characteristics

General subject characteristics (distribution and frequency) can be seen on Table 1. General characteristics are age, education level, partner's education level, and history of contraception usage before.

Table 1. Characteristics of subjects by age, education, parity, and history of contraceptive use (n = 30)

Variable	
Age (years)*	
• Mean**	31.6 ± 5.5
• Median†	32.5 (20 - 40)
Education (n.%)	
• Elementary school	6 (20.0)
• Junior high school	6 (20.0)
• Senior high school	16 (53.3)
• Bachelor degree	2 (6.7)
Parity (n)†	2 (1 - 5)
History of contraception (n.%)	
• Injections	18 (60.0)
• Pills	5 (16.7)
• implants	3 (10.0)
• IUD	1 (3.3)
• Others	1 (3.3)
• Never	2 (6.7)

* *Normality test of Kolmogorov-Smirnov and Shapiro-Wilk (p = 0.164)*
** *Mean ± SD*
† *Median (Minimum-Maximum)*

It can be seen that on average subjects' age was 31 years old (31.6 ± 5.5 year), with the youngest age of 20 years old and the oldest of 40 years old. Statistically, distribution of subjects' age using Kolmogorov-Smirnov and Shapiro-Wilk test was normal (p > 0.05), with a p value of 0.146.

All subjects had formal education, mostly senior high school level (53.3%). Most were well educated enough (above Junior Highschool) because only 20% subjects finished their education to elementary school.

All subjects to still in marriage and generally had two children, with the smallest parity of one, and the biggest of five. All subjects still wanted to have another child or wasn't sure to terminate their fertility. Because of those reasons, they were willing to use Monoplant® for three years.

Most of the subjects (93.3%) had used contraception before this research, and stopped for six years or more. The chosen contraception was hormonal (86.7%), 10% of them had used six capsules of implant, Norplant®.

Levonorgestrel Concentration

LNG examination (Table 2.) was done in two different laboratories: Makmal Terpadu FMUI-Cipto Mangunkusumo Hospital, Jakarta, Indonesia and Population Council New York, USA. All subjects' serum for LNG examination from the 1st month to the 6th month was examined in Makmal. Only a part of subject's serum (from the 3rd to the 6th month) was examined in USA because left serum amount was not sufficient to be transferred (at least 1 ml). The result, most of the LNG level serums examined in Makmal were low, but the concentration became higher if they were re-examined in USA. Statistically, distribution of LNG concentration (in Makmal and USA), using normality test of Kolmogorov-Smirnov and Shapiro-Wilk, howed normal data distribution (p > 0.05), with p = 0.085 for Makmal LNG concentration and p = 0.072 for USA LNG concentration.

On average, LNG serum concentration in Makmal laboratory after Monoplant® implant inserted was 237.5 pg/ml on the first month, above the concentration threshold of LNG (200 pg/ml; this concentration has contraceptive effect).[20] Then, on the 2nd month, the concentration doubled to 536.7 pg/ml, but with a wide range, 61.9 pg/ml to 1352 pg/ml, declining fast on the 3rd month to 176.6 pg/ml, dan then reducing slowly in the 6th month to 126.8 pg/ml. Because of that, after the 3rd month, LNG serum concentrations on average were under 200 pg/ml; moreover, it reached 19 pg/ml on the 6th month in one research subject. Vice versa, result of serum LNG concentration which was examined on USA laboratory stayed in high value, far above effective concentration.

Using Friedman test, changes in LNG concentration every month was statistically significant (p < 0.01). However, on post hoc analysis using Wilcoxon Signed Ranks, it showed that difference LNG concentration between the 1st and the 4th month (p = 0.271),

Table 2. Levonorgestrel concentration after Monoplant® implantation

LNG (pg/ml)	Lab. Makmal				Lab. USA			
	N	Mean	Min	Max	N	Mean	Min	Max
Month 1	30	237.5	36.6	520.1				
Month 2	30	536.7	61.9	1352.1				
Month 3	30	176.6	59.0	409.0	11	338.9	231.2	501.5
Month 4	30	195.1	46.6	510.5	8	424.8	287.5	608.3
Month 5	30	163.2	25.0	315.9	15	320.3	115.5	484.3
Month 6	29	126.8	19.0	277.0	13	337.5	187.5	532.8

and between the 3rd month and the 5th month (p = 0.185 to have a p value of > 0.05 which meant that there was no significant LNG serum concentration differences on those months.

Generally, although it has been seen that USA serum LNG concentrations were two times that of Makmal, linear regression analysis showed Adjusted R Square = 0.045, which meant that both USA and Makmal LNG serum concentration had a weak correlation power. So, LNG serum concentration measured in Makmal couldn't predict LNG serum concentration measurement in USA, and vice versa. If it was needed, LNG concentration analysis would be done for each group, Makmal result and USA result.

Sivin (1997) 32 in a multi center research (North and South America, Europe, and Asia) about Jadelle® revealed that progestin implant contraception effect depended on the diffusion ability of LNG from its reservoir to circulation system. Furthermore, LNG was circulating and bound to SHBG, and only free LNG gave effect to target organ.

A few moments after implant insertion, LNG could be detected in serum. Maximum concentration was achieved in 24 - 72 hours after insertion and would decline on the first week,[34] reaching median concentration on the first month,[32] and continuously decreasing in three years of usage.[33] LNG average serum concentration on the first month after Jadelle® insertion was 435 pg/ml and would decrease to 280 pg/ml by the end of third year. Although Jadelle® was only recommended for three years of contraception, this research was continued to 7 years. LNG serum concentration in the end of seventh year was 224 pg/ml.

Different from Sivin's research, Monoplant® does not show distribution of LNG concentration as discovered before, especially the 1st month concentration. Jadelle® LNG concentration which was usually very high on insertion (about 1000 pg/ml) and reached median concentration (about 500 pg/ml) in the end of the first month, did not show in Monoplant®. Monoplant® serum concentration in the end of the first month was only 237.5 pg/ml, and median concentration was reached on the second month (536.7 pg/ml), then LNG serum concentration would decrease gradually.

Not only LNG concentration distribution pattern looked different from Jadelle®, it's hard to explain the low LNG concentration on the first month (only one fourth of Jadelle® concentration) and how its concentration rose again on second month. Another thing was the range of result, which was very wide, especially in the second month, the lowest concentration was 61.9 pg/ml and the highest 1352 pg/ml (see Table 2). Although data distribution of Makmal LNG serum concentration was statistically normal, however, accuracy of examination result seemed to be low, so the data validity was also low.

Reviews about Makmal LNG low concentration had been done, presumably related to the lack of a functioning ß Counter machine. Although results of the QC (Quality Control) showed normal result, the enumerator couldn't read titanium isotope which had been used in this LNG examination series. Actually whole series of LNG concentration examination had been done properly according to the guidelines provided. LNG examination was done simultaneously for all serum collected from the 1st month to the 6th month. All serums were still in good condition, not one had lysis. Most of the examination process was done in Makmal, serum collection, storage, and counting, except for LNG extraction that was carried out outside out Makmal because the existing equipment was damaged. Because the low results of Makmal examination happened in nearly all subjects which presumably related to examination procedure, so statistically, the data obtained had a systematic error (systematic error, not random error). This systematic error was caused by weak internal validity (measuring instrument). The reliability test for Makmal data distribution was also low with Cronbach's alpha value = 0.371, data otherwise reliable if Cronbach alpha value is over 0.7.

Realizing there were mistakes in reading LNG concentration because of malfunctioning ß enumerators, the next LNG serum concentration examination were only carried out in Population Council Laboratories, New York, USA. Also, LNG data that will be discussed next are the data of LNG examination from USA lab.

Different from Makmal result (Table 2), LNG serum examination in Population Council Laboratories, New York, USA showed higher concentration, even in the sixth month, the average concentration was far above 200 pg/ml, exactly 337.5 pg/ml. average LNG concentration every month was relatively stable. There was no data about concentration on the first and second month, but LNG concentration in the following months were 338.9 pg/ml, 424.8 pg/ml, 320.3 pg/ml, and 337.5 pg/ml. Although there was a little fluctuation, changes statistically (Friedman test) showed no differences in levels of significance (p = 0.508).

Because LNG concentration at the end of the sixth month was above effective contraceptive level (200 pg/ml), reaching 337.5 pg/ml; even which was not much different from Jadelle® acceptor level of serum LNG in the same month, 357 pg/ml, then subjects could still use Monoplant® as contraception until the 36th month, as recomended. Another findings such as hormonal, blood chemistry, and other clinical findings will be delivered at the next discussion.

CONCLUSIONS

Levonorgestrel serum concentration in Monoplant® user until the sixth month is still far above contraceptive level.

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