A phase II study with a single implant contraceptive containing 3-ketodesogestrel (Implanon®): efficacy and safety

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Abstrak

Penelitian ini merupakan uji klinik fase II dengan tujuan untuk mengetahui daya guna (efektivitas) dan keamanan kontrasepsi Implanon®. Penelitian direncanakan berlangsung 2 tahun dengan kemungkinan diperpanjang menjadi 3 atau 4 tahun. Dari 200 subyek yang dipasang Implanon®, hanya 150 yang melanjutkan pemakaian pada tahun ketiga dan hanya 124 yang melanjutkan pemakaian pada tahun keempat. Tidak ditemukan kehamilan selama pemakaian Implanon® (658, 4 tahun wanita). Satu subyek menghentikan pemakaian karena amenorea (0,5%). Tidak ada penghentian pemakaian yang disebabkan oleh gangguan perdarahan. Pada umumnya keluhan subyektif yang dialami bersifat ringan (sakit kepala). Tidak ditemukan kelainan pada pemeriksaan fisik, ginekologi dan Pap smear. Tidak ditemukan peningkatan bermakna tekanan darah. Didapatkan kenaikan berat badan sebesar 2-7% setelah 1 tahun pemakaian. Disimpulkan bahwa Implanon® merupakan kontrasepsi yang efektif dengan efek samping normal.

Abstract

With the objective to find out the efficacy and safety of a single ethylene-vinyl-acetate (EVA) implant containing 3-ketodesogestrel, a phase II study was conducted in 200 women. The study planned for a two-year use with the possibility to extend the use to 3 or 4 years; 193 subjects completed 2 years, 150 subjects entered the third year and 131 subjects completed, 124 subjects entered the fourth year and 96 subjects completed. There was no pregnancy occurred in four years of use, a total exposure of 658.4 woman-years. One subject discontinued due to amenorrhoea (0.5%). None of the subjects discontinued for bleeding irregularities. A total of 4 subjects (2.0%) reported at least one side-effect. No serious side-effects were reported. Three (1.5%) subjects discontinued due to side-effects as primary reason. Side-effects that were considered drug-related were headache and dyspnoea (reported by two and one subjects, respectively). Six subjects once had a clinically significant low value for haemoglobin and for one subject this occurred twice during treatment. Except for "headache" and "dyspnoea" (reported twice and once, respectively), no clinically relevant shifts from normal to abnormal were reported with respect to physical examinations and gynecological evaluations. At implant removal, Pap smear class I was reported for all subjects but one (Pap II). No clinically significant values of systolic and diastolic blood pressure were observed. An effect on body mass index was indicated by a slight mean increase (about 2-7%) from the month 12 assessment onwards: an increase of 10% or more at any time-point was reported by 41 subjects (20.5%). It is concluded that the single implant contraceptive containing 3-ketodesogestrel is a highly effective contraceptive method with minimal side-effects.

Keywords: *Implanon®, implant contraceptive, efficacy, safety.*

Contraceptive implants are a successful method for long term prevention of pregnancy. With the development of synthetic polymers, it has become possible to develop hormonal delivery systems with long duration of action and continuous release of the drug. Advantages of the long-term contraceptive implants are lack of concern for compliance and prompt return of fertility after removal. Furthermore, the parenteral route of administration results in a lower metabolic burden on the liver than with oral contraceptives.[1-3]

NV Organon (Oss, The Netherlands) has developed a single-rod implant (Implanon®) with a length of 40 mm and a diameter of 2 mm, which is applied subdermally by a disposable sterile inserter. The rod is made of an ethylene vinyl acetate copolymer (EVA) with a core containing approximately 68 mg 3-ketodesogestrel or etonogestrel (ENG).

The initial release rate of the implant is approximately 67 µg/day which slowly decreases over time. The constant release profile results in sufficiently high plasma ENG concentration (>90pg/ml) to in-

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hibit ovulation for at least three years.[4,5]

ENG is a progestin, structurally derived from 19-nortestosterone, it is the biologically active metabolite of desogestrel (DSG). DSG is the progestin component of a number of widely used oral contraceptives with a well established efficacy and safety profile. The characteristics of the implant's EVA membrane, combined with the high specific progestin activity of ENG, allow the use of a single-rod system with a low and almost zero-order release. As a consequence of these properties, dose-related side-effects are minimized.

Subdermal implant containing pure progestins have been tested as hormonal contraceptives in several studies. Results of those preliminary short-term studies have encouraged further investigation.[4-7]

The trial presented here was carried out with ENG-EVA implant in order to assess effectiveness, side effects and length of the effective period.

MATERIALS AND METHODS

Characteristics of subjects

Two hundred women were recruited in the study. The inclusion criteria were age between 18 and 40 years, sexually active and of childbearing potential, good physical and mental health, normal cycles with a length of 24-35 days and a variation of ≤ 3 days, ability and willingness to accurately fill in the diary card with information on bleeding, accept the implant as the sole method of contraception, willing to return to the clinic at the stipulated time points, and willing to give informed written consent.

The exclusion criteria were: pregnancy, breast feeding, within two weeks after an abortion, before the first menses after delivery, use of an injectable or implant hormonal method of contraception within a period of six month or the use of other hormonal contraceptives within a period of two months, history of ectopic pregnancy, past or present endocrine disorder, haemoglobin (Hb) less than 10 g/dl, breast discharge (other than lactation), past or present disturbance of liver function i.e. cholestatic jaundice, a history of jaundice of pregnancy or jaundice due to previous (oral) contraceptive use, Rotor syndrome or Dubin Johnson syndrome, history of hyperlipoproteinaemia, hypertension i.e. systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg, use of one or more of the following drugs: sex steroids, hydantoins, barbiturates, primidone, carbamazepine, rifampicin and griseofulvin, a history of (within 12 months) alcohol or drug abuse, and administration of investigational drug within 3 months prior to this study.

Characteristics of implant

Implanon® is a single-rod implant with a length of 40 mm and a diameter of 2 mm containing approximately 68 mg of ENG. The rod is made of EVA with an ENG surrounded by an EVA membrane. The initial release rate of ENG from Implanon® is approximately 67 µg/day.

Implanon® was delivered in the needle of a sterile, disposable, specially designed inserter individually packed in an aluminium sachet. The sachets were labelled with the protocol number, storage conditions, information on content of sachet, expiry date, packing number and the subject number.

Procedure for insertion

In normal cycling women insertion of the implant was performed between the first and the fifth day of the subject's menstrual flow. The subjects randomly assigned into two groups: group A and group B. In group A, the subjects were given a small amount of local anaesthetic (1 ml of 1% lidocaine). In group B, the subjects were not given local anaesthetic. The area of insertion was thoroughly cleansed with an antiseptic prior to insertion.

Implanon® was to be inserted on the inside of the upper (non-dominant) arm, 6 to 8 cm above the elbow in the groove between the biceps and triceps (sulcus bicipitalis medialis).

The inserter was entered through the subdermal layer to the full length of the needle. The seal of the inserter was broken by pressing the plunger support. The plunger was turned 90 or 180 degrees. While the plunger was fixed against the arm, the inserter was slowly pulled out of the arm. A pressure bandage with sterile gauze was applied to minimize.

Procedure for removal

The implant was located by palpation. The subject's arm was washed and antiseptic applied. A small amount of local anaesthetic (0.5 ml 1% lidocaine) was applied under the implant. After making a 2 mm incision, the implant was gently pushed toward the incision until the tip was visible. The implant was then grasped with forceps and removed. If the im-

Table 1. Flow chart of the study

	Time in month	Assessment	Status implant site	Bweight B.P	Pelvic exam	Physical exam	Pap test	Hb
Screening	-1	I						
Year 1	0	II	*					
	3	III	*	*				
	6	IV	*	*		*		*
	9	V	*					*
	12	VI	*	*		*		*
Year 2	15	VII	*					
	18	VIII	*	*				*
	21	IX	*					
	24	X	*	*	*	*	*	*
Year 3	27	XI	*					
	30	XII	*	*		*		
	33	XIII	*					
	36	XIV	*	*	*	*	*	*
Year 4	39	XV	*					
	42	XVI	*	*		*		
	45	XVII	*					
	48	XVIII	*	*	*	*	*	*

plant could be pushed into the incision, closed forceps were inserted into the incision in order to gently dissect the tissues around the implant. While the tissues were being dissected, the implant was pushed toward the incision. After removal of the implant, the incision was closed and bandaged as discussed under 'Procedure for insertion'.

Design of the study

If a subject met all entry criteria and a written informed consent form was signed, screening assessment were to be done. Results of the assessments had to be available before implantation.

The experimental flow of the study after completion of the screening assessment is demonstrated in Table 1. The implant was to remain in situ for 24, 36 or 48 months, depending on the willingness of the volunteers to give their consent to the extension of the study. Assessments were scheduled at 3-month intervals during the study. To allow some flexibility to the subjects, a 1-month deviation was allowed. During the whole study period occurrence of adverse experiences as well as use of concomitant medication were to be reported. If suspected at any time in the study, a pregnancy test was to be performed. Data on the subjects' bleeding pattern were to be recorded by the subject on a daily basis in a diary card. These data were to be transcribed on the daily bleeding form in the Case Report Form (CRF). During the first two years, subjects were also asked to return on a monthly basis to exchange diary cards. Prior to implant removal a blood sample was drawn from the arm not bearing the implant for ENG measurement. The concentrations were used to evaluate pharmacokinetics of the implants. Result are reported separately.

RESULTS

Profile of the subjects

The profile of the subjects are described in Table 2. Age ranged from 20 to 35 years old with mean 28.3 years (SD 3.7).

The mean body weight was 49.8 ± 8.1 kg, while the mean height was 154.0 ± 4.7 cm. Making the mean Body Mass Index 21.0 ± 3.0 kg/cm^2. All the subjects have already experienced at least one delivery. More than 39% of them being para 3 or above. With regard to last contraceptive method use being 65.5% IUD and 30% of them had used no method at all.

Table 2. Profile of subjects (N=200)

Profile		Mean ± SD	%
Age (years)		28.3 ± 3.7	
Height (cm)		154.0 ± 4.7	
Body weight (kg)		49.8 ± 8.1	
Body Mass Index (kg/cm2)		21.0 ± 3.0	
Parity :	1-2		60.5
	3-		39.5
Last Contraception:	- None		30.0
	- Pill		1.5
	- Implantables		1.0
	- Injectables		1.0
	- IUD		65.5
	- others		1.0

Efficacy

Table 3. Events and cumulative numbers of termination and continuation

Type of Termination	Year-1	Year-2	Year-3	Year-4
Pregnancy	0	0	0	0
Amenorrhea	1	1	1	1
Bleeding irregularities	0	0	0	0
Other medical	0	1	2	3
Planning pregnancy	1	3	16	39
Other personal	1	2	7	11
Lost to follow up	0	0	0	0
Total termination	3	7	26	54
No.of subjects entering the year	200	197	150	124
No.of subjects completing the year	197	193	131	96

There was no pregnancy occurred during the four-year use (Table 3), making the life table cumulative discontinuation rate at year 4 for pregnancy among users of Implanon® is 0.0 per 100 women-years.[8]

The number of subjects who completed the study or discontinued method is shown in Table 3. A total of 197 subjects completed year-1 and continued to year-2; 193 subjects completed year-2.

Only 150 subjects agreed to continue to use the method in year-3 and 131 subjects completed year-3. In year-4 124 subjects agreed to continue to use the Implanon® as contraceptive method and 96 subjects completed year-4. There was no subject lost to follow up.

Table 4. Net cumulative termination and continuation rates per 100 women.

Type of Termination	Year-1	Year-2	Year-3	Year-4
Pregnancy	0.0	0.0	0.0	0.0
Amenorrhea	0.5	0.5	0.5	0.5
Bleeding irregularities	0.0	0.0	0.0	0.0
Other medical	0.0	0.5	1.0	1.5
Planning pregnancy	0.5	1.5	10.7	27.2
Other personal	0.5	1.0	3.5	5.5
Total termination	1.5	3.5	15.7	34.7
Continuation	98.5	96.5	84.3	65.3
No. of women-year	197	386.0	505.8	658.4

Acceptability

The continuation rates are shown in Table 4, being year-1: 98.5%, year-2: 96.5%, year-3: 84.7% and year-4: 65.3%.

Reasons for discontinuation

In the year-1 there were 3 subjects (1.5%) discontinued the method use being one subject due to planning pregnancy and one subject due to personal reason.

In the year-2 there were four more subjects discontinued the method being 1 subject due to other medical reason, 2 subjects due to planning pregnancy and 1 subject due to other personal reason making cumulative numbers of termination being 7 or 3.5%.

There were 19 more subjects terminated the implant use in the year-3, 13 of them due to planning pregnancy, 5 due to other personal reasons and 1 due to other medical reasons.

The cumulative number of termination in year-3 was 26 (15.7%). Another 13 subjects terminated the use in year-4, 1 subject terminated due to other medical reason and 4 subjects terminated due to other personal reasons. Cumulative number of termination in year-4 was 54 (34.7%).

Bleeding irregularities and amenorrhoea

There was no subject terminated the contraceptive use due to bleeding irregularities, however there was one subject terminated the contraceptive use due to amenorrhoea.

Other medical reasons

There were 3 subjects discontinued the use of Implanon® due to medical reasons being 2 due to headache and 1 due to dyspnoea.

Non medical reasons

A total of 39 subjects discontinued for planning pregnancy and a total of 11 subjects discontinued due to other personal reasons.

- Weight gain
  The weight gain during 4 year study in shown in the increasing of body mass index being 0.3 ± 0.7 kg/cm^2 in year-1; 0.8 ± 0.9 kg/cm^2 in year-2; 0.1 ± 1.0 kg/cm^2 in year-3 and 1.5 ± 1.3 kg/cm^2 in year-4. There was no subject discontinued due to weight gain.

- Blood pressure changes
  There was a small mean decrease in systolic blood pressure of 0.4 mmHg in year-1 and 0.3 mmHg in year-2; mean decrease in diastolic blood pressure of 0.8mmHg in year-1 and 0.9 mmHg in year-2.

However there was a slight mean increase in year-3 and year-4 being 1.0 and 1.0 mmHg for systolic and 1.3 and 0.5 for diastolic. There was no subject discontinued due to blood pressure changes.

Vaginal bleeding analysis

Completed vaginal bleeding record cards were obtained from the subjects throughout the study. The vaginal bleeding patterns as determined by analysis of these records will be described in other paper.

Insertion and removal

The experience of insertion and removal with Implanon® will be reported in other paper.

DISCUSSION

This phase II, efficacy and safety, study provided a total of 658.4 woman-years of Implanon® use. With regard to contraceptive efficacy there was no pregnancy occurred due to method failure.[8,9] This result reflects the main mechanism of action of Implanon® i.e. inhibition of ovulation.[5-7]

The continuation rate for year-1, year-2, year-3 and year-4 were 98.5%, 96.5%, 84.3% and 65.3% respectively. Originally, the study was planned to evaluate Implanon® for two years. Therefore the subjects had already been informed started from the beginning that the Implanon® study lasted for two years. And then during the study it was amended to continue the evaluation up to four years. Many subjects had already planned to have the Implanon® removed after year-2. This is the reason why the continuation rates for year-3 and year-4 dropped to 84.3% and 65.3% respectively. With regard to reasons for discontinuing the method there was no subject discontinued due to bleeding irregularities and only one subject discontinued due to amenorrhoea. There was no subject lost to follow-up. Other than headache and dyspnoea which accounted for discontinuation of 3 subjects, no other medical reasons given by the subjects for discontinuing the method. A very high proportion of discontinuers were due to non medical reasons i.e. for planning pregnancy and other personal reasons. None of them could be considered as the indirect side-effect of Implanon®. Many times non-medical reasons given by subjects who wish to discontinue the method even though they may not be the real reasons for discontinuation[9].

It is concluded that Implanon® is a highly effective contraceptive method with minimal side-effects.

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