Available online at www.sciencedirect.com

SCIENCE DIRECT®

Contraception

Contraception 70 (2004) 379–382

Original research article

Effect of etonogestrel subdermal contraceptive implant (Implanon®) on liver function tests — a randomized comparative study with Norplant® implants

Arijit Biswas[a,*], Sinjini Biswas[b], Osborne A.C. Viegas[a]

[a]*Department of Obstetrics and Gynaecology, National University Hospital, National University of Singapore, 119074, Singapore*
[b]*Faculty of Medicine, University of Melbourne, Victoria 3010, Australia*

Received 22 April 2004; revised 17 May 2004; accepted 31 May 2004

Abstract

Objective: The study aimed to assess the possible differences in effects of Implanon® and Norplant® implants on liver function over 2 years of use.
Methods: This is a 2-year open randomized study of 80 implant (Implanon® and Norplant®) acceptors. Selected parameters of liver function were tested in the serum before implant insertion and at 6, 12 and 24 months after implant insertion.
Results: In both the implant groups, the mean total and unconjugated bilirubin and the gamma-glutaryl transferase levels were significantly raised during implant use. For none of the subjects, at any sampling period, did the levels exceed the normal range in our population. There was no significant elevation of any other liver enzymes in either group.
Conclusion: It appears that there may be mild hepatocellular dysfunction associated with the use of both Implanon® and Norplant®, which is possibly of no clinical significance to the healthy acceptor.

Keywords: Implanon®; Etonogestrel; Norplant®; Implants; Progestins; Liver function

1. Introduction

Implanon® (NV Organon, Oss, The Netherlands) is the newest contraceptive implant system which has become available in many countries around the world. It is a single rod that contains a core of 68 mg of etonogestrel (3-keto-desogestrel), the biologically active metabolite of desogestrel, with a membrane of ethylene vinyl acetate. Inhibition of ovulation occurs within 1 day of implant insertion, and effective contraception lasts for 3 years. Fertility returns within 1 month after implant removal. Implanon®, being a single-rod system, has a simple insertion and removal procedure. Prior to Implanon®, the only other widely marketed implants were the levonorgestrel-releasing six-capsule system, Norplant®, and the two-rod system, Jadelle. The safety and efficacy of the levonorgestrel-releasing implants are well established.

We have previously evaluated the effects of Implanon® implants on carbohydrate metabolism, thyroid and adrenal function and serum lipids [1–3]. The metabolic effect of this implant has been found to be minimal [4]. However, very little data are available on its effect on liver function. The objective of the present study was to assess and compare the effects of Implanon® and Norplant® contraceptive implants on selected parameters of liver function. Except for a short study over a 6-month period [5], no other study has evaluated liver function in Implanon® users.

2. Subjects and methods

Eighty healthy female volunteers were recruited for the study. Screening for hepatitis B surface antigen was done before the subjects were recruited to the study and only screen-negative subjects were eligible for the study. Institutional Review Board approval was obtained prior to the commencement of the study. A written informed consent was obtained and a detailed patient information

* Corresponding author. Tel.: +65 6776 4261; fax: +65 6779 4753.
E-mail address: obgab@nus.edu.sg (A. Biswas).

0010-7824/$ – see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2004.05.011

Table 1
Subject characteristics

	Implanon®		Norplant®	
	Mean	SD	Mean	SD
Age (years)	29.1	4.6	29.2	3.9
Weight (kg)	58.1	11.1	56.5	8.3
Height (cm)	157.7	5.1	156.4	4.9
BMI (kg/m^2)	23.3	3.9	23.1	3.5

sheet with contact number of the principal investigator was provided to each subject. The volunteers were randomized to receive either Implanon® or Norplant® implants, with 40 subjects in each arm. Randomization was performed through a computer-generated allocation table with the group numbers put into sealed opaque envelopes. The study period was 24 months. The sizes of the study and control groups are based upon the recommendations made by WHO for metabolic studies, namely, 40 subjects per group [6]. Blood samples were drawn prior to the insertion of the implant and after 6, 12 and 24 months of use. The samples were obtained from fasting subjects, from the antecubital vein contralateral to the arm in which the implant or implants were inserted. The parameters evaluated were: total bilirubin and unconjugated fraction; albumin; liver enzymes, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and lactate dehydrogenase (LDH).

Total and unconjugated bilirubin were estimated using simple photometry. For albumin, the bromocresol green dye binding method was used. The Johnson & Johnson Vitros system was used for these measurements (Ortho-Clinical Diagnostics, Johnson & Johnson, Rochester, NY, USA). The liver enzymes were measured by a rate assay method using the same Johnson & Johnson Vitros system. Hepatitis B surface antigen was detected using the microparticle enzyme immunoassay technique by the AXSYM system (Abbott Laboratories, Abbott Park, IL, USA).

2.1. Statistical methods

Based on the preliminary data from the study by Egberg et al. [5], a sample size of 80 subjects that entered in this two-treatment parallel design study would have a probability of 84% (power=0.84) of detecting a treatment difference, at a two-sided 5% significance level, if the true difference between the treatments is 0.674 times the standard deviation. The software from the Massachusetts General Hospital Biostatistics Centre (http://hedwig.mgh.harvard.edu/biostatistics/index.html) was used for power calculation. Without assuming normalcy of distribution, nonparametric tests of significance were used to analyze the results. In each treatment group, comparison of changes

Table 2
Liver function test parameters

Parameter	Implanon®					Norplant®					p-value[a]
	Absolute				% change from baseline	Absolute				% change from baseline	Group comparison of mean
	N	Mean	SD	p-value[b]		*N*	Mean	SD	p-value[b]		
Total bilirubin (μmol/L)											
Pre-Insertion	40	3.42	1.64			40	2.25	0.54			.001
6 months	39	6.71	4.18	.000	108.31	37	5.75	4.92	.000	149.54	.050
12 months	39	9.59	3.95	.000	215.42	36	9.58	4.76	.000	331.71	.717
24 months	37	9.32	4.32	.000	196.01	31	9.26	3.98	.000	317.20	.975
Unconjugated bilirubin (μmol/L)											
Pre-Insertion	40	1.17	0.71			40	1.25	0.54			.794
6 months	39	5.07	4.56	.000	374.36	37	4.64	4.99	.000	364.86	.311
12 months	39	8.59	3.95	.000	706.76	36	8.58	4.75	.000	725.81	.717
24 months	37	8.32	4.32	.000	720.09	31	8.25	3.98	.000	758.33	.975
ALT (U/L)											
Pre-Insertion	40	23.80	11.85			40	23.80	8.14			.546
6 months	39	20.94	14.90	.089	− 7.14	37	17.94	5.00	.000	−19.46	.983
12 months	39	23.61	12.69	.576	7.10	36	15.30	3.29	.000	−30.31	.000
24 months	37	22.89	12.55	.687	2.60	31	18.93	9.92	.008	−15.83	.041
AST (U/L)											
Pre-Insertion	40	21.3	9.41			40	21.60	7.06			.334
6 months	39	23.74	8.70	.032	21.02	37	19.16	3.79	.214	−6.95	.007
12 months	39	23.33	8.88	.065	19.93	36	20.05	4.32	.160	−2.56	.152
24 months	37	20.59	6.74	.402	5.23	31	21.77	7.31	.749	4.67	.367

[a] Results of Mann–Whitney *U* test (two unrelated samples nonparametric test) on group differences.
[b] Results of Wilcoxon matched-pair signed-rank test on change from baseline.

Table 3
Liver function test parameters

Parameter	Implanon®					Norplant®					p-value[a]
	Absolute				% change from baseline	Absolute				% change from baseline	Group comparison of mean
	N	Mean	SD	p-value[b]		*N*	Mean	SD	p-value[b]		
Alkaline phosphatase (U/L)											
Pre-Insertion	40	66.50	43.03			40	67.70	17.36			.129
6 months	39	60.05	20.00	.504	−3.59	37	65.78	18.77	.018	−3.95	.169
12 months	39	59.25	17.24	.376	−1.93	36	63.91	19.68	.006	−6.08	.364
24 months	37	59.51	18.63	.431	−4.33	31	63.06	19.64	.006	−3.11	.509
GGL (U/L)											
Pre-Insertion	40	25.05	19.52			40	18.60	6.00			.039
6 months	39	33.69	27.91	.000	37.38	37	21.94	8.25	.001	22.80	.002
12 months	39	33.00	26.03	.000	38.67	36	23.16	6.89	.000	32.04	.008
24 months	37	33.10	28.78	.000	36.06	31	24.83	7.52	.000	38.28	.229
LDH (U/L)											
Pre-insertion	40	449.35	152.47			40	387.97	66.59			.006
6 months	39	511.92	137.51	.001	18.47	37	405.54	58.37	.091	5.74	.000
12 months	39	488.23	125.80	.001	14.56	36	392.25	59.20	.665	1.43	.000
24 months	37	436.05	85.02	.441	2.43	31	401.90	120.32	.890	2.74	.010

[a] Results of Mann–Whitney *U* test (two unrelated samples nonparametric test) on group differences.
[b] Results of Wilcoxon matched-pair signed-rank test on change from baseline.

from baseline was performed for each assessment and for the last measurement using the Wilcoxon matched-pairs signed-rank test. Mann–Whitney *U* test was used for between-group comparisons of means.

3. Results

There was no significant difference in the mean age, body weight and body mass index (BMI) between the two study groups (Table 1). Three subjects (7.5%) in the Implanon® group and nine subjects (22.5%) in the Norplant® group discontinued during the study. No subject in the Implanon® group discontinued due to bleeding irregularities as the primary reason compared to four in the Norplant® group. In the Norplant® group, three women discontinued due to nonmenstrual adverse experiences and two discontinued for personal reasons. In the Implanon® group, one discontinued due to nonmenstrual adverse experience, one due to a perceived change in libido and a third subject migrated out of the country. Summary statistics for absolute values, changes from baseline and relative changes from baseline of liver function test parameters are presented.

In both implant groups, the most significant change was seen in the mean total and unconjugated bilirubin levels. At the end of 2 years of use, the mean unconjugated bilirubin levels were more than sevenfold greater than the mean pre-insertion levels for users of both types of implants (Table 2). However, for none of the subjects, at any sampling period, did the total and unconjugated bilirubin levels exceed the normal range in our population.

The ALT levels were significantly decreased in the Norplant® group, while there was no appreciable change in the Implanon® group. On the other hand, the AST and LDH levels were significantly increased in the Implanon® users during the first year of use which gradually returned

Table 4
Serum albumin concentrations

Parameter	Implanon®					Norplant®					p-value[a]
	Absolute			% change from baseline		Absolute			% change from baseline		
	N	Mean	SD	Mean	Median	*N*	Mean	SD	Mean	Median	
Albumin (g/L)											
Baseline	40	45.70	3.11			40	44.78	2.19			
Month 6	39	46.28	3.91	1.36	2.04	37	46.03	3.03	3.06	2.33	.560
Month 12	39	46.82	3.05	2.48	2.27	36	46.31	2.30	3.45	4.35	.671
Month 24	37	46.27	3.40	1.14	2.22	31	47.06	2.61	4.64	4.35	.083
Last measurement	39	46.41	3.40	1.55	2.22	37	46.89	2.63	4.68	4.35	.063

[a] Results of the Wilcoxon test on the percentage of change from baseline.

towards pre-insertion values at 2 years. There was no consistent change in the levels of these two liver enzymes in Norplant® users. Alkaline phosphatase levels decreased slightly in both groups, although the reduction was only statistically significant in the Norplant® group (Table 3). The decrease was noted at all assessment periods following implant insertion. In both groups, the GGT levels were significantly raised during implant use. The magnitude of the rise varied from 22.8% to 38.7% above the pre-insertion baseline values (Table 3). Up to 1 year, the rise was significantly more in the Implanon® users compared with the Norplant® users.

There were no significant changes in serum albumin levels during the course of the treatment in either of the implant groups (Table 4).

4. Discussion

Although the liver is not a classical target organ for sex steroids, it is influenced by sex steroids in numerous ways. This is true for both its morphological and functional aspects. The liver is inevitably more involved when the steroids are administered orally due to the first-pass effect after ingestion. In non-enteral forms of steroidal contraception, for example, injectables, implants, and others, the impact on hepatic metabolism is less pronounced.

Long-term studies with levonorgestrel implants, Norplant® and Jadelle, have shown that besides a significant increase in serum bilirubin, there are no other significant changes in liver function to suggest possible hepatocellular dysfunction at the end of 5 years [7–10]. Bala et al. [11] reported that there were no changes in hepatic transaminases on short- or long-term use of Jadelle (Norplant®-2). It appears from these studies that, for levonorgestrel implants, despite changes in some tests of liver function, values remained within the normal ranges for the populations studied. These data are consistent with studies of the impact of progestin-only pills, particularly those with norgestrel, on liver function [12].

In their comparative study of Implanon® and Norplant® users, Egberg et al. [5] evaluated liver function in both groups over a 6-month period only. Increases in total bilirubin and GGT and decreases in transaminases (ALT and AST) were observed for both Norplant® and Implanon® users. The effect of Norplant® on bilirubin was significantly greater than that of Implanon®. The other changes were not significantly different between the two groups. Despite the changes observed, the authors reported that the mean values "in general were well within the laboratory reference range" for all tests, and no individual using Implanon® had clinically noteworthy values.

In our study as well, a significant rise in total and unconjugated bilirubin level was observed in both Implanon® and Norplant® users. In both groups, the rise was significant from the 6 months assessment onwards. No significant difference was observed between the groups in the hepatic transaminases (AST and ALT) and in ALP levels. There was a significant increase in GGT levels, in both groups of implant users, noticeable from 6 months onwards. However, the raised mean levels of bilirubin and GGT remained within the normal range for the local population.

It appears that there may be mild hepatocellular dysfunction associated with the use of both Implanon® and Norplant®, which is possibly of no clinical consequence to the healthy acceptor. However, the increase in bilirubin reported in some populations, including ours, during both Norplant® and Implanon® use, although not outside the normal ranges for these populations, could become relevant for some individuals. Therefore, it is advisable that caution should be exercised in using these implants in women with preexisting liver disease.

Acknowledgments

The authors would like to thank Ms. Jamila Beevi, the study coordinator, and the staff of the Fertility Control Center, National University Hospital, Singapore, for their support and help.

References

[1] Biswas A, Viegas OAC, Coeling Bennink HJT, Korver T, Ratnam SS. Effect of Implanon® use on selected parameters of thyroid and adrenal function. Contraception 2000;62:247–51.
[2] Biswas A, Viegas OAC, Coeling Bennink HJT, Korver T, Ratnam SS. Implanon® contraceptive implants — effects on carbohydrate metabolism. Contraception 2001;63:137–41.
[3] Biswas A, Viegas OAC, Roy AC. Effect of Implanon® and Norplant® subdermal contraceptive implants on serum lipids — a randomized comparative study. Contraception 2003;68:189–93.
[4] Dorflinger LJ. Metabolic effects of implantable steroid contraceptives for women. Contraception 2002;65:47–62.
[5] Egberg N, van Beek A, Gunnervik C, et al. Effects on the hemostatic system and liver function in relation to Implanon® and Norplant®. A prospective randomized clinical trial. Contraception 1998;58:93–8.
[6] Michal F. Safety requirements for contraceptive steroids. UK: Cambridge University Press; 1989. p. 439 [Published on behalf of WHO].
[7] Shaaban MM, Elwan SI, El-Sharkawy MM, Farghaly AS. Effect of subdermal levonorgestrel contraceptive implants, Norplant®, on liver function. Contraception 1984;30:407–12.
[8] Shoupe D, Mishell DR. Norplant®: subdermal implant system for long-term contraception. Am J Obstet Gynecol 1989;160:1286–92.
[9] Singh K, Viegas OAC, Loke DFM, Ratnam SS. Effect of Norplant® implants on liver, lipid and carbohydrate metabolism. Contraception 1992;45:141–53.
[10] Singh K, Viegas OAC, Loke D, Ratnam SS. Effect of Norplant®-2 rods on liver, lipid and carbohydrate metabolism. Contraception 1992;45:463–72.
[11] Bala Y, Dhall GI, Majumdar S. Short-term and long-term effects of Norplant®-2 on plasma lipoproteins and glucose tolerance. Adv Contracept 1991;7:77–83.
[12] McCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review. Contraception 1994;50(Suppl):S1–195.