LONG-LASTING OVULATION INHIBITION WITH A NEW INJECTABLE PROGESTAGEN ORG-2154

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ABSTRACT

A new long-acting injectable progestagen was tested in 15 women who volunteered for the study. The occurrence of ovulation was assumed by the elevation of progesterone levels above 2ng/ml following a pre-ovulatory estradiol peak. Following a 200mg injection, ovulation was inhibited in all 15 women for five to ten months. In four subjects the interval between the injection and the first progesterone peak was five months. For eight, the interval was six to eight months. In the other three women, ovulation occurred more than eight months following injection. Bleeding episodes, similar to menstruation, occurred in most patients. Bleeding intervals lasting longer than 45 days occurred in nine subjects but more prolonged amenorrhea lasting longer than 60 days was reported by only five subjects. Blood chemistry which included blood cell counts, cholesterol, glucose, alkaline phosphatase, transaminases, urea nitrogen and creatinine remained within normal limits throughout the treatment.

INTRODUCTION

Despite the advantages of injectable contraceptives such as long-lasting effect, ease of administration and reversibility, their use in family planning programs remains relatively low. One of the reasons for this lack of interest is probably related to the restrictions imposed by the United States Federal Drug Administration on the use of medroxyprogesterone (Depo-Provera), the only long-acting injectable contraceptive in widespread use today. Norethisterone enanthate which was introduced more recently turned out to be less effective than Depo-Provera because it is less potent and requires a relatively short interval between injections (1). We have reported recently on a new long-acting 19-nor steroid derivative which appears to inhibit ovulation for a longer period of time than medroxyprogesterone acetate (2). The compound, whose structure is shown in Figure 1, is the dodecanoate of 16-alpha-ethyl-21-hydroxy-19-norpreg-4-ene-3,20-dione (ORG-2154). Ovulation was inhibited in all of the six patients receiving a single injection of either 150mg or 200mg of the drug. The duration of the effect in patients receiving 150mg was 60 to 120 days, whereas, in three women who received 200mg, ovulation was inhibited for 120 to 200 days. The present study which extends those observations reports on 15 volunteers who received 200mg of ORG-2154.

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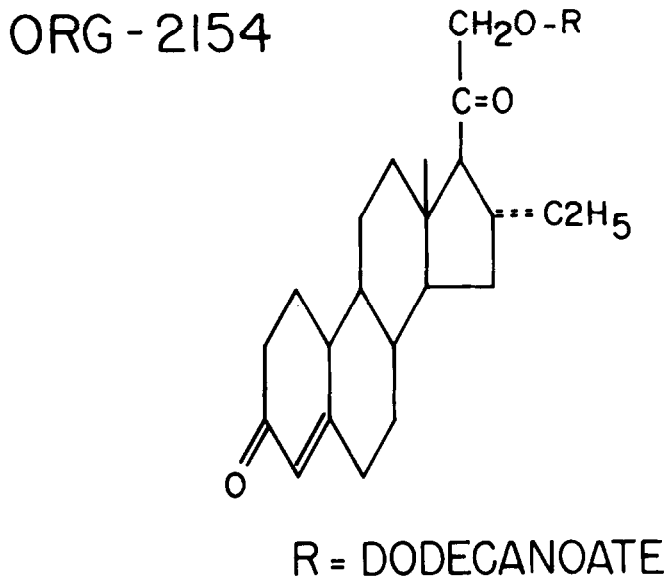

Figure 1. Structural formula of ORG-2058 (16-alpha-ethy-21-hydroxy-19-norpreg-4-ene-3,20-dione). ORG-2154 is the dodecanoate of ORG-2058, substitution taking place in R.

MATERIALS AND METHODS

Fifteen women, 20-36 years of age, volunteered for the study. Estradiol and progesterone blood levels were measured twice or three times weekly for one full control cycle and throughout the treatment period, which was estimated to last six to nine months. A dextran-coated charcoal radioimmunoassay (RIA) which requires only a simple diethyl ether extraction of serum prior to assay was used (3,4). Treatment consisted of a single intramuscular injection containing 200mg of ORG-2154 (16-alpha-ethyl-hydroxy-19-norpreg-4-ene-3,20-dione-21-dodecanoate), in oil solution (arachis oil + 5% benzyl ancohol), given on day 5 of the cycle.

Complete blood cell counts, cholesterol, glucose, alkaline phosphatase, transaminases, urea nitrogen and creatinine were measured before and during the treatment.

RESULTS

Following the injection of 200mg of ORG-2154, no elevation of progesterone was detected for a period of five to nine months. In four subjects the interval between the injection and the first rise in progesterone was five months, in eight it was six to eight months, and in two it lasted between eight and nine months. In one subject the first rise in progesterone occurred 10 months following the injection of ORG-2154. Table I shows the interval in days between the injection and the first elevation of progesterone above 2ng/ml for each of the subjects. Estradiol peaks were inhibited for the first two months following the injection but returned gradually to the normal cyclic pattern to reach normal blood levels of 150 to 600Pg/ml one week preceding the first post-injection progesterone peak. Figures 2,3, and 4 illustrate the changes in both progesterone and estradiol levels in patients injected with 200mg of ORG-2154. Bleeding episodes similar to menstruation usually occurred following an estradiol peak. Bleeding intervals lasting longer than 45 days occurred in nine subjects but prolonged amenorrhea lasting longer than 60 days occurred in five subjects. Menstrual patterns of the 15 patients are shown in Figure 5. Blood cell counts, cholesterol, glucose, alkaline phosphatase, transaminases, urea nitrogen and creatinine remained within normal limits in all subjects throughout the treatment period.

DISCUSSION

The active component in ORG-2154 is 16-alpha-ethyl-21-hydroxy-19-norpreg-4-ene-3,20-dione (ORG-2058), a potent progestagen which has a 5.6 times higher affinity for progesterone receptors than progesterone. Its binding to glucocorticoid receptors is negligible (5). Because of this specificity, ORG-2058 is currently used as an ideal radioligand for the assay of progesterone receptors in tissues (6).

Two esters of ORG-2058 have been tested as potential long-acting progestagens. The oenanthate (ORG-2793) revealed strong progestational properties in several species which included the rat, the guinea pig, and the rhesus monkey. However, because it is quickly hydrolized in the body, its action is relatively short-lived. The dodecanoate (ORG-2154), on the other hand, seems to be hydrolized very slowly allowing sustained release of ORG-2058 over a long period of time. Unpublished studies carried out by Organon (OSS,

TABLE I

Interval between 200mg i.m. injection of ORG-2154 and the first progesterone rise in days

Patient Nº	Days
1	213
2	166
3	161
4	250
5	209
6	287
7	307
8	225
9	138
10	167
11	203
12	211
13	203
14	222
15	186

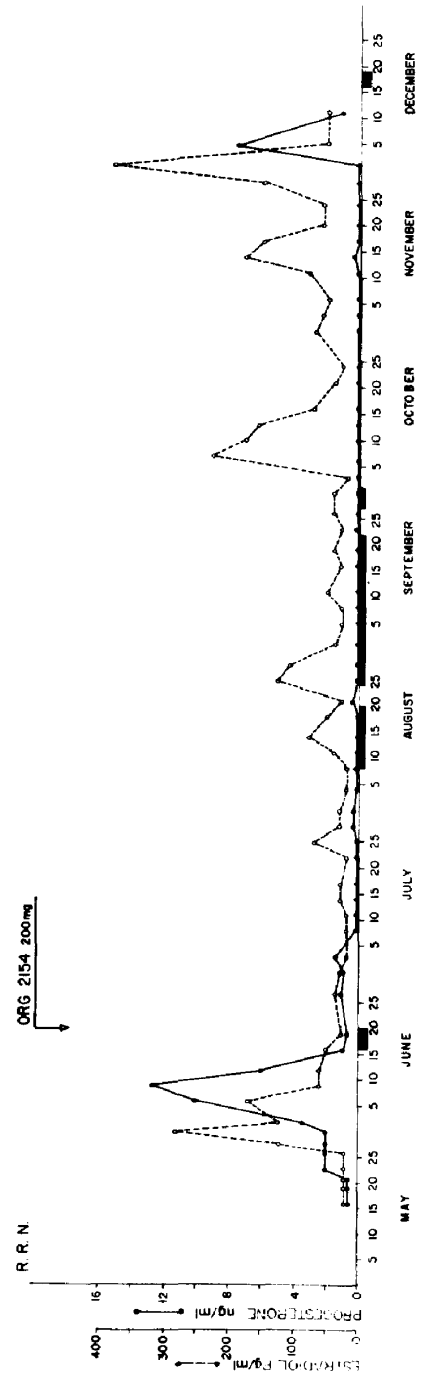

Figure 2, The effect of ORG-2154 on estradiol and progesterone blood levels in one woman treated with 200 mg of the compound. Note that the rise in progesterone indicating the occurrence of ovulation takes place six months after the injection. Bars on the baseline indicate uterine bleeding.

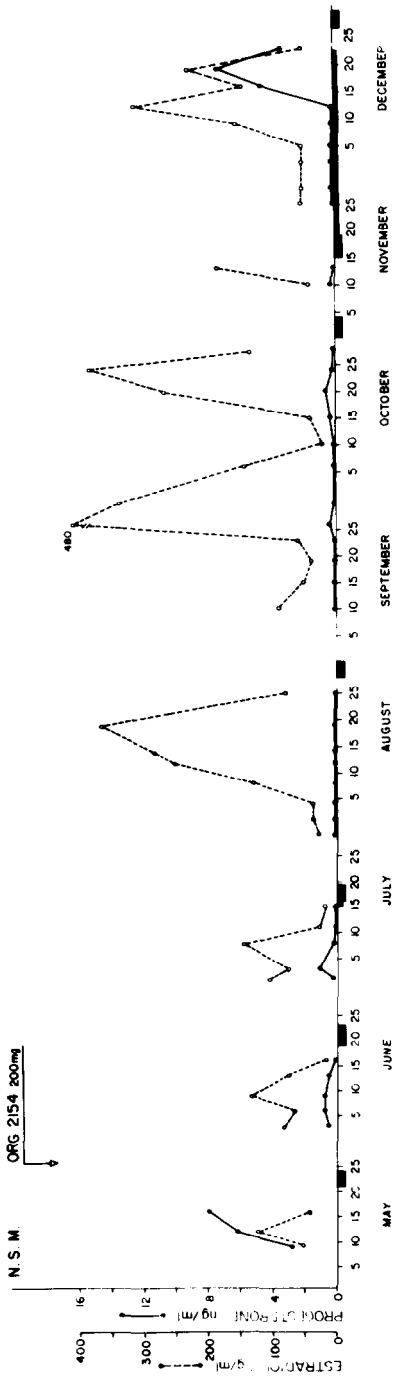

Figure 3. The effect of ORG-2154 on estradiol and progesterone blood levels in one woman treated with 200 mg of the compound. Note that the rise in progesterone indicating the occurrence of ovulation takes place seven months after the injection. Bars on the baseline indicate uterine bleeding.

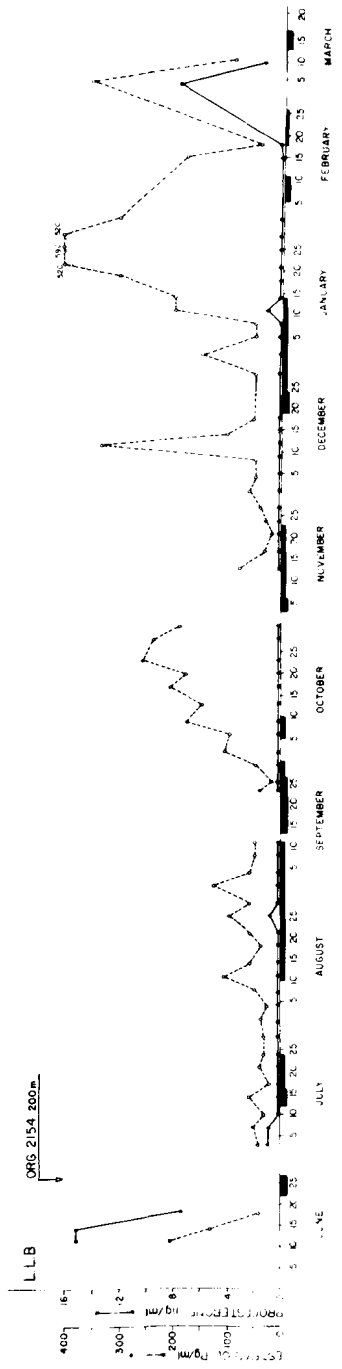

Figure 4 The effect of ORG-2154 on estradiol and progesterone blood levels in one woman treated with 200 mg of the compound. Note that the rise in progesterone indicating the occurrence of ovulation takes place eight months after the injection. Bars on the baseline indicate uterine bleeding.

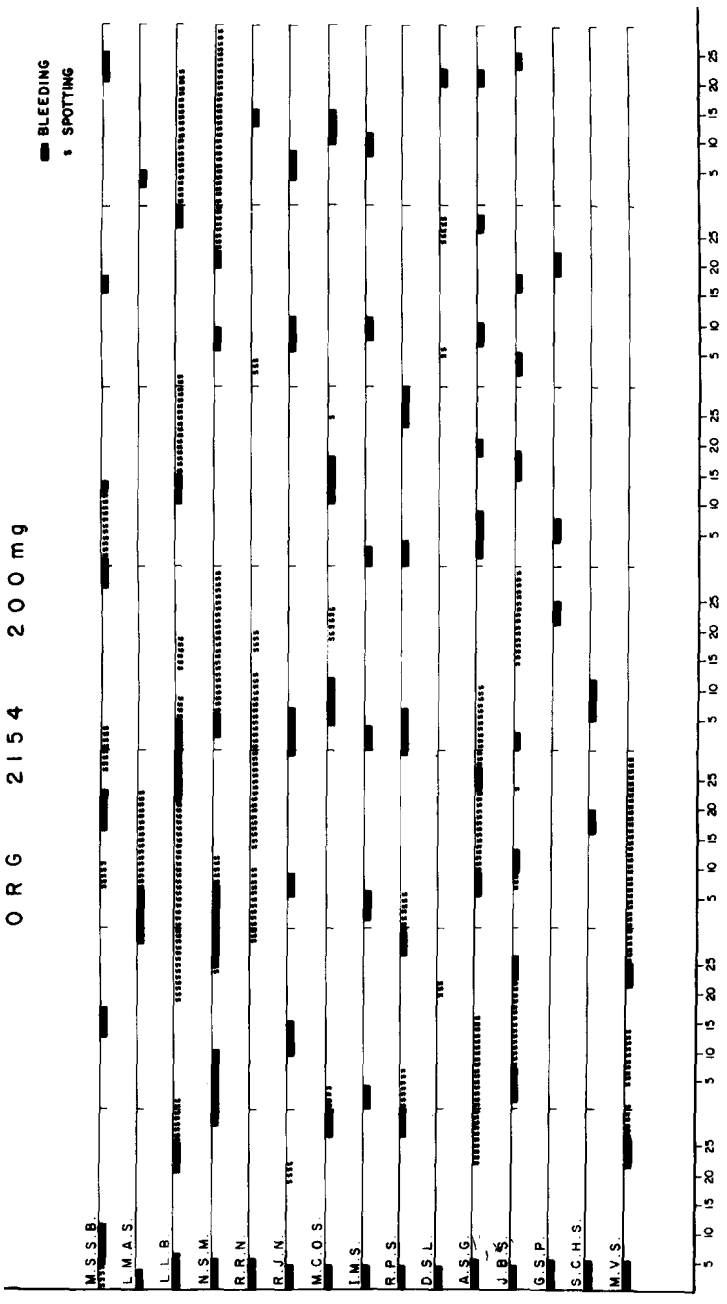

Figure 5. Bleeding patterns of subjects following one single intramuscular 200mg injection of ORG-2154.

Holland) in baboons and rhesus monkeys indicated that ORG-2154 has a half-life five times longer than ORG-2793.

Endocrine profiles of women treated with ORG-2154 indicated that following one single 200mg injection, ovulation was inhibited for four to seven months. The duration of the effect appeared to be dose-related since at a dose of 150mg, ovulation was inhibited for no longer than two to four months (2). The present study in a larger group of women shows that, in fact, inhibition of ovulation following administration of a single injection of ORG-2154 lasts from more than four months up to ten months. Fifty percent of the women ovulated approximately six months following the injection of ORG-2154. Three women had shorter ovulation inhibition intervals of five months and in only one subject was the interval shorter than five months. In two women ovulation was inhibited for eight months but in one it lasted the longest interval of ten months.

The present series confirms the previous findings that the long-acting inhibition of ovulation induced by ORG-2154 compares favorably with medroxyprogesterone (Depo-Provera) which requires twice the dose of ORG-2154 to produce the same effect (7,8). It was shown in rabbits that following the administration of Depo-Provera, plasma levels of the progestin were detected only up to 100 days, whereas, following the administration of ORG-2154, the parent compound (ORG-2058) could be detected in plasma for more than 180 days (9).

Of interest for the potential use of ORG-2154 as a contraceptive is the menstrual-like character of the periodic bleeding which follows the injection of the compound. Unlike other ovulation inhibitory compounds, ORG-2154 does not suppress cyclic estrogen secretion allowing for periodic bleeding, which may be, in some patients, very similar to menstruation. Bleeding episodes follow estrogen peaks as in normal menstruation. Endometrial shedding is limited to a few days because the endometrium is under the progestational dominance of ORG-2154.

In view of its long-acting effect and tolerance, ORG-2154 has the potential to be developed as an injectable contraceptive to be used in both developed and underdeveloped countries.

ACKNOWLEDGEMENTS

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