A PRELIMINARY PHARMACOLOGICAL TRIAL OF THE MONTHLY INJECTABLE CONTRACEPTIVE CYCLOPROVERA

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ABSTRACT

A comparative pharmacological pilot study of the monthly injectable contraceptive CycloProvera was carried out in 11 women in four centres. There were no significant differences in the results between the centres except that the injection-bleeding interval appeared to be shorter in Swedish women than in those in Havana and Mexico. Medroxyprogesterone acetate was detectable in blood for 28 to 62 days after injection of CycloProvera and although follicular activity returned in less than 28 days after injection in many of the women, corpus luteum function was suppressed for at least seven weeks in all women. Most of the women retained a regular menstrual pattern; six of 33 cycles were amenorrhoeic. There was no significant change in any of the biochemical and haematological analyses.

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CONTRACEPTION

INTRODUCTION

Several combinations of synthetic oestrogens and gestagens have undergone preliminary clinical trials as monthly parenteral contraceptives (1, 2). Only two of these combinations have been tested more extensively; of these the first Deladroxate (dihydroxyprogesterone acetophenide 150 mg and oestradiol oenanthate 10 mg) is no longer available. The second CycloProvera (medroxyprogesterone acetate 25 mg and oestradiol cypionate 5 mg) is widely used in some countries (3) and reports (4, 5, 6, 7, 8) of clinical trials of this formulation have been published. In view of this and the interest of the World Health Organisation in developing a monthly injectable formulation, a preliminary pharmacological trial of CycloProvera was undertaken to ascertain its effect on menstruation, on ovarian function, on a number of biochemical and haematological analyses and on the plasma levels of the injected steroids. No information regarding the latter two aspects has been previously reported.

MATERIALS AND METHODS

Clinical material

Four centres (the WHO Collaborating Centres for Clinical Research in Alexandria, Havana and Mexico and the WHO Collaborating Centre on Research and Training in Human Reproduction, Stockholm) participated in the trial; each recruited three subjects. Only healthy female volunteers aged 21 to 40 years were admitted to the trial. They were required to have had regular menstrual cycles of 26 to 32 days in length during the 12 months prior to recruitment and to have had three regular menses after discontinuing the use of oral contraceptives or an IUD. The nature of the study and the effects of the drug were explained to the subject, her willingness and ability to abide by the protocol were ascertained and her consent for inclusion in the trial was obtained. A full medical history and physical examination were then carried out. Women were excluded if they had previous history of thromboembolic disorders, recent or severe liver disease, suspected breast or other genital malignancies, if pregnancy was suspected or if any of the laboratory tests described in the Results section were abnormal. Women who were suitable for inclusion in the trial were given a diary card on which to record episodes of menstrual bleeding and requested to return to the clinic within four days of the onset of the next period of menstruation.

Preparation administered

CycloProvera (1 ml aqueous microcrystalline suspension containing 25 mg medroxyprogesterone acetate and 5 mg oestradiol cypionate, Upjohn, Kalamazoo, USA) was given by deep intragluteal injection between days 1 and 5 of the menstrual cycle with the subsequent two injections being given at 28-day intervals.

Table I. Details of women enrolled in the trial (Values shown are ranges)

Centre	Age (y)	Height (cm)	Body weight (kg)
Alexandria	36 - 39	155 - 168	62 - 76
Havana	24 - 32	152 - 174	73 - 76
Mexico City	28 - 38	158 - 164	69 - 76
Stockholm	31 - 39	158 - 170	57 - 78

Design of investigation

Subjects were studied for one cycle prior to administration of drug, during three months when the drug was injected and for a further two months after treatment. Blood samples were taken weekly throughout the trial for the estimation of oestradiol and progesterone by radioimmunoassay. In samples collected during the three treatment months, the concentration of medroxyprogesterone acetate was also measured by radioimmunoassay (9). Between days 20 and 23 of the control cycle and thereafter at monthly intervals, blood samples were taken for biochemical and haematological analyses. Between days 20 and 23 of the control cycle and of the third injection month, an endometrial biopsy was taken and a glucose tolerance test carried out. Blood pressure and body weight were recorded at each weekly visit.

RESULTS

The mean ages, heights and body weights at the beginning of the trial for the groups of subjects are shown in Table I. Two subjects gained more than 3 kg during the trial and one subject lost more than 3 kg. There was no significant change in blood pressure in any subject during the trial.

Effect of CycloProvera on ovarian function

The control pretreatment cycles were ovulatory in the subjects studied in Alexandria, Mexico and Stockholm as shown by the increases in blood levels of both oestradiol and progesterone. During the treatment period serum oestradiol levels were elevated during the first few days after injection because of the injected oestradiol cypionate (Figure 1). Ovulation was suppressed during the treatment period as shown by the low levels of progesterone; in no subject did the plasma progesterone concentration exceed 3 ng/ml during the treatment period. However in some subjects there was evidence from the rise in blood oestradiol levels to values in excess of 150 pg/ml for the occurrence of follicular activity towards the end of the injection interval (Table II). This was particularly noticeable in subject S1 who showed increased oestradiol levels 22 and 26 days after the first injection (293 and 736 pg/ml, respectively), 24 days after the second (469 pg/ml) and 21, 24 and 27 days after the third (335-693 pg/ml) and in subject S3 who showed an increase to 195 pg/ml on day 25 of the first injection period and to 242 pg/ml and 246 pg/ml at the end of the second and third injection periods, respectively. The oestradiol levels of subject M2 21 days after the second injection and of subject A2 at the end of the first injection period were above 200 pg/ml.

Although follicular activity returned in three subjects within four weeks of the third injection and in all within 50 days, plasma progesterone levels suggested that luteal activity was not present until more than seven weeks after the last injection (Table II).

Table II. Return of ovarian activity in women receiving CycloProvera (Figures show earliest time in days after third injection for occurrence of follicular activity, assessed by a plasma oestradiol 150 pg/ml, and of luteal activity, assessed by a plasma progesterone level 3 ng/ml)

Subject	A1	A2	H1	H2	H3	M1	M2	M3	S1	S2	S3
Follicular activity	33	33	—	—	28	50	40	—	21	49	28
Luteal activity	—	—	—	—	—	78	82	48	63	79	55

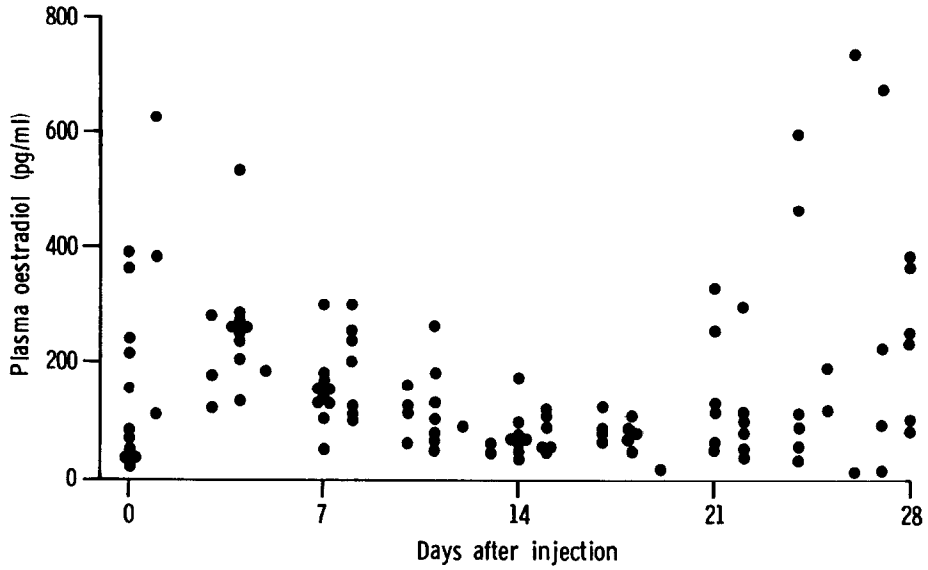

Figure 1. Serum estradiol concentrations at various times after injection of CycloProvera.

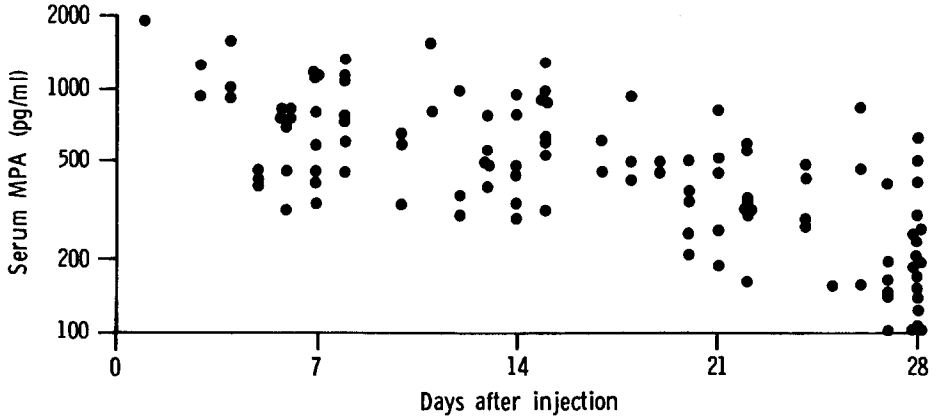

Figure 2. Serum medroxyprogesterone acetate concentrations at various times after injection of CycloProvera on Day 0.

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