PHARMACOKINETIC STUDY OF DIFFERENT DOSES OF DEPO PROVERA

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ABSTRACT

Doses of DepoProvera of 25, 50, 100 and 150mg were administered to four groups of women. The mean time for the return of follicular and luteal activity increased with increasing dose of DepoProvera. Luteal activity was suppressed for a longer period than follicular activity. None of the women receiving the two higher doses of DepoProvera showed a return of luteal function within 100 days of injection. The period for which medroxyprogesterone acetate (MPA) was detectable in serum increased with increasing dose but the values for the 100 and 150mg doses were not significantly different. There was a significant correlation between the concentration of MPA in blood and the return of follicular and luteal function. It is suggested that in the population studied, 100mg DepoProvera would be as effective as the usual 150mg dose and that injection of 50mg DepoProvera would provide a contraceptive effect for two months. The dose of MPA in the monthly injectable CycloProvera could be substantially reduced without loss of effectiveness.

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CONTRACEPTION

INTRODUCTION

DepoProvera, a microcrystalline suspension of medroxyprogesterone acetate, has been widely used as an injectable contraceptive (1). The failure rate using an injection of 150 mg every 90 days is less than 0.1 per 100 women-years. However, a number of studies have shown that MPA may still be detectable in the circulation in many women for more than 90 days after injection of this dose and in some women MPA was detectable for more than 200 days after injection (2, 3, 4). This high circulating level of MPA leads to prolonged suppression of pituitary, and hence ovarian, activity and is probably the cause of the high incidence of amenorrhoea seen in women using DepoProvera. Almost all of the pharmacokinetic studies of DepoProvera have been carried out in Caucasian women and it might be expected that in other ethnic groups, usually of lower body weight, the dose of DepoProvera could be considerably reduced without any loss of efficacy. No information is available on levels of MPA in blood after administration of doses of DepoProvera lower than 150 mg or the effect of lower doses on ovulation. In the present study, groups of Thai women were treated with doses of DepoProvera of 25, 50, 100 and 150 mg and the effect of these doses on ovulation suppression and on menstruation was determined and correlated with the levels of MPA in blood.

SUBJECTS AND METHODS

Volunteer subjects were obtained from women attending a Thai Family Planning clinic who had opted to use an injectable contraceptive. The aim of the study was explained to the women and written consent for their participation was obtained. The women were between 24 and 36 years in age with regular menstrual cycles for six months preceding entry into the trial. None had been pregnant within 120 days or lactating within 60 days prior to admission into the trial. All subjects had a full clinical examination before entering the study and none had any contraindications to the use of a steroidal contraceptive. Since the contraceptive efficacy of doses of DepoProvera below 150 mg could not be guaranteed, women using lower doses were advised to use a barrier method of contraception.

Four groups each of five women were studied. The women were randomly allocated to these groups. The women in each group received 25, 50, 100 or 150 mg DepoProvera as a deep intramuscular injection in the gluteal region between days 4 and 6 of a menstrual cycle. Subjects were studied for one cycle prior to injection and up to six months after injection. Blood samples were taken twice weekly. Each subject was given a record card on which to record episodes of bleeding and the card was used also to indicate the days on which the subject was to attend for blood sampling.

After sampling, the blood was allowed to clot at room temperature, then centrifuged and the serum removed. The serum was deep frozen and transported to London frozen in dry ice where each sample was analysed by radioimmunoassay for the levels of medroxyprogesterone

acetate (5), oestradiol and progesterone. Quetelet's index (weight in Kg divided by square of height in metres) was calculated (6).

RESULTS

Details of the subjects enrolled in the trial are shown in Table I. There was no significant difference between the women in each of the four groups in respect of age, height and body weight. Two women in Group 50 and one each in Groups 100 and 150 had values for Quetelet's index above the upper limit (24 units) of the 'desirable range'(7). All subjects showed a rise in the plasma oestradiol or progesterone levels during the control cycle, indicating that ovulation had occurred.

Effect of DepoProvera on ovarian function

The duration of the suppressive action of the various doses of DepoProvera on ovarian function as assessed by plasma levels of oestradiol and progesterone is indicated in Table I. A rise in the plasma oestradiol level greater than 150 pg/ml was taken to indicate the presence of follicular activity and luteal activity was presumed to be present when the plasma progesterone level exceeded 3 ng/ml.

The mean time for the return of follicular function increased with increasing doses of DepoProvera and varied from 41.2 days in Group 25 to 59.6 days in Group 50, 77 days in Group 100 and 110 days in Group 150. There was no significant difference between Groups 25 and 50, 50 and 100 and 100 and 150 in the time required for the return of follicular activity. However, there were significant differences in the return of follicular function between Groups 25 and 100 ($P < 0.05$), between Groups 25 and 150 ($P < 0.01$) and between Groups 50 and 150 ($P < 0.05$). Inhibition of follicular activity for more than 90 days occurred in all except one of the subjects in Group 150, in two subjects in Group 100 but in none in Groups 25 and 50. In six subjects (A, E, F, L, O and U) the return of follicular activity was associated with a broad peak of elevated oestradiol levels extending over a period of 20 to 50 days. None of these peaks was associated with a rise in the plasma progesterone level.

For eight subjects (B, G, H, K, N, P, S and V) the occasion on which follicular activity first returned was followed by a rise in the plasma progesterone level indicating that ovulation occurred as soon as follicular function returned (Table I), whereas in the majority of subjects the first evidence of follicular function was not followed by a rise in the plasma progesterone level indicating that ovarian follicular activity returned some considerable time before luteal activity. This suppression of luteal function was particularly lengthy in subjects receiving the two higher doses of DepoProvera. For these women, none showed a return of luteal activity within 100 days of injection whereas all except two of the 10 women in Groups 25 and 50 showed a return of luteal function within this time. The differences between Groups 25 and 50 and between Groups 100 and 150 in the time of return of luteal function were not significantly different, but there were significant differences between Groups 25 and 100 ($P < 0.01$), between Groups 50 and 100 ($P < 0.05$), between Groups 25 and 150 ($P < 0.01$) and between Groups 50 and 150 ($P < 0.01$).

Table I. Details of subjects receiving various doses of DepoProvera and changes in ovarian function.

Subject	Age (y)	Body wt(Kg)	Height (cm)	Quetelet's index	Days after injection for plasma oestradiol (E) or progesterone (P) to show significant rise	
					E	P
DMPA 25 mg						
A	36	53	162	20.2	36	81
B	35	62	166	22.5	50	53
C	25	59	158	23.6	29	> 50
D	27	57	158	22.8	29	81
E	36	47	157	19.1	62	108
Mean	31.8			21.8	41.2	74.6
SD	5.4			1.7	14.4	23.8
DMPA 50 mg						
F	33	51	159	20.2	64	120
G	29	61	151	26.7	83	86
H	31	60	160	23.4	58	65
J	30	65	147	30.1	41	94
K	29	53	150	23.6	52	55
Mean	30.4			24.8	59.6	94.3
SD	1.7			3.7	15.6	27.2
DMPA 100 mg						
L	34	65	156	26.7	50	148
M	31	46	153	19.6	71	137
N	24	50	162	19.1	95	102
O	29	53	160	20.7	57	148
P	35	59	156	24.2	112	123
Mean	31.3			22.1	77.0	131.6
SD	3.9			3.3	26.0	19.5
DMPA 150 mg						
R	34	63	154	26.6	119	155
S	33	56	153	23.9	97	104
T	36	62	161	23.9	> 167	> 167
U	35	48	157	19.5	66	157
V	30	45	149	20.3	101	107
Mean	33.6			23.1	110.0	136.6
SD	2.3			2.4	37.1	27.5

For eight women follicular activity returned while MPA was still detectable in blood but in no woman did luteal function return until MPA was undetectable. For the remaining ten women (omitting subjects C and T), follicular activity returned between 3 and 37 days (mean 20.2 days) after serum MPA became undetectable whereas luteal function did not return until 14 to 109 days (mean 44 days). The time of return of ovarian function in relation to the uptake and metabolism of DepoProvera is shown in Fig. 1. There was a statistically significant correlation ($P < 0.05$) between the time after injection at which serum MPA levels became undetectable (Y) and the time of return (X) of follicular and luteal activity. The equation for the regression line with respect to follicular activity was $Y = 0.43X + 33.7$ and that for luteal activity was $Y = 0.46X + 13.8$.

Metabolism of medroxyprogesterone acetate

Mean values for the plasma concentration of MPA of the four groups of women at varying times after injection are shown in Fig. 2 and other information relating to the metabolism of DepoProvera is summarised in Table II. The mean value for the highest serum MPA concentration detected at any time after injection increased with increasing doses of DMPA, but as shown in Table II, there was a considerable variation in the individual values. Whereas only two of the subjects in Groups 100 and 150 had levels less than 4 ng/ml, only three of the women in Groups 25 and 50 had values higher than this. However, these results must be interpreted with caution since samples were collected only twice weekly and the day on which the highest MPA concentration actually occurred may have been missed. However, the days for which MPA was detectable in serum, i.e., a concentration greater than 100 pg/ml, increased as the dose of DepoProvera administered increased up to 100 mg. Although there was no significant difference between the two lower doses or between the two higher doses in the number of days for which MPA was detectable in the circulation (Fig.?), there was a statistically significant difference between the two lower doses compared with the two higher does ($P < 0.01$).

When the plasma MPA levels for each subject were plotted semi-logarithmically against time after injection, approximately straight lines were obtained. As expected there was a highly significant correlation between the plasma MPA levels and time after injection in all subjects as shown by the values for the correlation coefficient R (Table II). The values for the slope of these regression lines is also shown in Table II and represent the rate at which MPA was taken up from the injection site and metabolised. If it is assumed that the rate of metabolism of MPA in the subjects was similar and not dependent on the dose of DepoProvera injected, then the value for the slope is related to the rate of uptake from the injection site. The higher values for the slope in subjects taking the two lower doses indicate a relatively more rapid uptake than in subjects receiving the two higher doses. However, there was a considerable between subject variation in the value for the slope and the mean value for Group 25 was not significantly different from that of Group 150. The value for the constant B (Table II) which represents the plasma MPA concentration assuming instantaneous distribution increased with the dose of DepoProvera injected but only the differences between the two lowest dose groups and Group 150 were statistically significant ($P < 0.05$).

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