

Original research article

# Comparative pharmacokinetics and pharmacodynamics after subcutaneous and intramuscular administration of medroxyprogesterone acetate (25 mg) and estradiol cypionate (5 mg)

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## Abstract

**Background:** The efficacy of contraceptives is affected by its route and ease of administration. Herein, both pharmacokinetics and pharmacodynamics of the once-a-month combined injectable contraceptive medroxyprogesterone acetate (MPA) plus estradiol cypionate (E<sub>2</sub>-Cyp) were compared after intramuscular (IM) or subcutaneous (SC) injection in women of reproductive age.

**Study Design:** Thirty women were randomly assigned to the SC ( $n=15$ ) or IM ( $n=15$ ) route of MPA 25 mg+E<sub>2</sub>-Cyp 5 mg administration. Serum samples were obtained daily for 7 days and then three times a week for 40 days in order to quantify E<sub>2</sub>, progesterone and MPA. In addition, three ultrasounds were performed on each subject to determine follicular development, and a daily record of the bleeding pattern and side effects was maintained.

**Results:** A comparative analysis showed that the main pharmacokinetic (peak serum concentration, peak serum time, area under the serum concentration vs. time curve, absorption half-life and elimination half-life) and pharmacodynamic parameters, such as follicular development and ovulation, were similar in the SC vs. IM groups. Complete suppression in ovarian function was present in all women. The bleeding patterns and side effects were similar in both groups.

**Conclusions:** The results presented herein demonstrate that the injection of 25 mg of MPA plus 5 mg of E<sub>2</sub>-Cyp has similar efficacy and safety with either the SC or IM route of administration. The SC option can be considered a viable self-administered contraceptive option that might increase women's compliance to contraceptive use.

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**Keywords:** Pharmacokinetics; Pharmacodynamics; Medroxyprogesterone acetate; Estradiol Cypionate; Intramuscular and subcutaneous

## 1. Introduction

Low-dose monthly injectable contraceptives were introduced worldwide in the late 1980s. The two formulations marketed were Mesygina, a combination of norethindrone enantate plus estradiol valerate (NET-EN 50 mg+E<sub>2</sub>-Val 5 mg), and Cyclofem, a combination of medroxyprogesterone

acetate plus estradiol cypionate (MPA 25 mg+E<sub>2</sub>-Cyp 5 mg) [1–3]. The estradiol esters contained in these combinations are of short- and medium-term action since, for about 15 days, they produce high serum levels, which subsequently decline resulting in uterine bleeding about 3 weeks after the injection [4].

The once-a-month combined injectable contraceptives are highly effective. The cumulative pregnancy rate for 100 women-years is 0.4 with NET-EN 50 mg+E<sub>2</sub>-Val 5 mg and from 0 to 0.2 for 100 women-years with the combination MPA 25 mg+E<sub>2</sub>-Cyp 5 mg [1–5]. Because of the short time

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in clearing MPA from circulation, ovulation and fertility are recovered 60–90 days after the last injection [5,6].

The main mechanism of action of the monthly injectable contraceptives is the inhibition of ovulation by progestin negative feedback on the hypothalamic–pituitary axis. They also produce changes in cervical mucus and in endometrial structure [5].

A subcutaneous (SC) version of depot medroxyprogesterone acetate (DMPA, Depo-subQ) is now available and has shown comparable efficacy and safety when compared to the intramuscular (IM) route of administration. The SC formulation may have potential advantages, including increased convenience and ease of administration. The fact that the new form of administration eliminates the need for women to periodically return to their health care provider for subsequent injections might increase women's compliance and acceptance of this contraceptive method [7–9].

The objective of this study was to compare the pharmacokinetics and pharmacodynamics of two routes of administration of the once-a-month combined contraceptive MPA 25 mg plus E<sub>2</sub>-Cyp 5 mg (an IM or SC injection) in women on the fifth day of their menstrual cycle.

## 2. Material and methods

Sexually active Mexican women between 18 and 35 years of age and wishing to participate in the study were recruited from the family planning clinic at the Isidro Espinosa de los Reyes National Institute of Perinatology, where they were provided contraceptive services. Additional inclusion criteria included regular menstruation (with an average cycle length of 25–35 days) during the 3 months before enrollment and a body mass index (BMI) of 20–28 kg/m<sup>2</sup>. Exclusion criteria included breastfeeding, being pregnant or at risk for pregnancy, having a vaginal infection or sexually transmitted disease, having contraceptive implants, having used oral contraceptives during the last 3 months, having used hormone-medicated intrauterine devices or any other hormonal medication in the previous 2 months, having contraindications to the use of a contraceptive with MPA+E<sub>2</sub>-Cyp or having received some injectable contraceptive DMPA-IM during the previous 6 months [10].

The present study was an experimental, comparative, randomly assigned study in women volunteers. Thirty women were randomly allocated into one of two groups ( $n=15$ ) by a randomization table; this number of subjects is considered to have sufficient power to provide information on the actual pharmacodynamics and pharmacokinetics study based on prior experiences in previous studies with a similar design [11,12]. An evaluation was made of the pharmacokinetics and pharmacodynamics of SC and IM injection of MPA 25 mg and E<sub>2</sub>-Cyp 5 mg (manufactured and provided by Importadora y Manufacturera Bruluart, Tultitlan, State of Mexico). The drugs were administered in sterile syringes with 25-gauge×16-mm or 22-gauge×32-mm needles for both SC or IM administration, respectively. Women received a single injection on the

gluteus region for the IM group or on the upper arm for the SC group on the fifth day of their menstrual cycle. All subjects gave their written informed consent to participate in the study in accordance to the principles of the revised Declaration of Helsinki. The study was approved by the Institutional Ethics Committee for compliance with good clinical procedures.

Before admitting a woman into the study, several assessments were made. Medical, gynecological and drug anamneses were obtained. Physical and gynecological examinations were performed. Blood samples (5 mL) for the determination of MPA, estradiol (E<sub>2</sub>) and progesterone (P<sub>4</sub>) were obtained on the day just before injection (on day 5 of menstrual cycle, equal to day 0 of the study) and after the injection on days 1, 2, 3, 4, 5, 6, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34 and 37. Serum was obtained and stored frozen at –80°C prior to being assigned.

A solid-phase competitive chemiluminescent enzyme immunoassay on the Immulite analyzer (Siemens Medical Solutions Diagnostics, Malvern, PA, USA) was used for the quantitative measurement of E<sub>2</sub> and P<sub>4</sub> in serum. Intraassay and interassay coefficients of variation (CVs) for E<sub>2</sub> at 0.25, 0.64 and 3.5 nmol/L did not exceed 8.0%. For P<sub>4</sub>, the CVs at 5.0, 8.5 and 48 nmol/L did not exceed 12%. The assay sensitivity for E<sub>2</sub> was 0.04 nmol/L; and for P<sub>4</sub>, 0.3 nmol/L.

For the quantitative measurement of MPA, a conventional extraction radioimmunoassay (RIA) technique was performed following the manufacturer's instructions (Immunometrics, London, UK). Serum samples (0.2 mL) were extracted with diethyl ether (2 mL). The extract was dried under nitrogen atmosphere and redissolved in 0.5 mL of phosphate buffer (pH 7.4). The redissolved extract was assayed for MPA by a tritiated RIA with a charcoal separation technique [13]. The assay sensitivity for MPA was 0.4 nmol/L, and the interassay CV did not exceed 23% at 0.9 nmol/L; these CVs decrease until 17% at the dose of 5.1 nmol/L.

During their follow-up visits, subjects were questioned about treatment-related adverse side effects. All women used a menstrual diary card for the systematical reporting of their bleeding cycle [14]. The classifications of bleeding intensity included 'no bleeding,' 'spotting' (defined as vaginal bleeding not requiring sanitary protection) and 'bleeding' (defined as vaginal blood loss for which sanitary protection was needed).

Ovulation was considered to have occurred if the P<sub>4</sub> level was >9 nmol/L. Three pelvic ultrasound procedures were performed for each woman, one between 20 and 24 days after injection, another between 25 and 29 days and the last between 30 and 35 days, all with a scanner in real time and vaginal transducer of 3.5 MHz (Ultramark-4 Advanced, Advance Technology Laboratories, USA). Follicular growth greater than 20 mm was considered as a preovulation follicle.

Descriptive statistics and comparative analysis of the average age, weight, height and BMI, as well as previous pregnancies, childbirths, cesareans and abortions, were performed by means of a Wilcoxon rank-sum test. Comparative treatment-related adverse effects of the IM and SC

administration were performed by the Fisher's Exact Test. A  $p$  value  $< .05$  was considered statistically significant.

Analysis of serum concentration vs. time was performed for the two administration routes. The following pharmacokinetic variables were assessed for the rate of absorption: peak serum concentration ( $C_{max}$ ), peak serum time ( $T_{max}$ ) and the area under the serum concentration vs. time curve (AUC) obtained by the trapezoidal method. Absorption half-life ( $T_{1/2abs}$ ) and elimination half-life ( $t_{1/2el}$ ) were also determined. The pharmacokinetic parameters of IM and SC routes of administration were compared by the unpaired Student's  $t$  test. A  $p$  value  $< .05$  was considered statistically significant. The WinNonlin® Professional, version 5.1.1 (Pharsight Corporation, Mountain View, CA, USA), was used for obtaining the pharmacokinetic parameters and for the graphical presentation of the data for individual subjects. SPSS for Windows, version 15 (SPSS, Chicago, IL, USA), was used to perform the unpaired  $t$  test and non-parametric analyses.

### 3. Results

All 30 women were randomly allocated into one of two groups of 15 each. All except one completed the study. A subject from the IM group withdrew from the study because she received an incomplete dosage. Table 1 shows the clinical characteristics of the women admitted to the study. No significant differences ( $p > .05$ ) were observed among groups.

The results of the three vaginal ultrasounds performed after the IM or SC administration indicated that only one subject showed signs of follicular development (from the SC group and in the second ultrasound at 21 days after injection) but did not reach preovulatory dimensions (19 mm) and did not reach ovulation (serum progesterone  $< 1.5$  nmol/L). All other women showed no sign of follicular maturation or ovulation throughout the injection interval.

The means  $\pm$  SD of serum  $E_2$  are depicted in Fig. 1A. No significant differences were observed between either route of administration. Endogenous  $E_2$  levels began to rise in both groups by days 30–34 postinjection. Serum progesterone

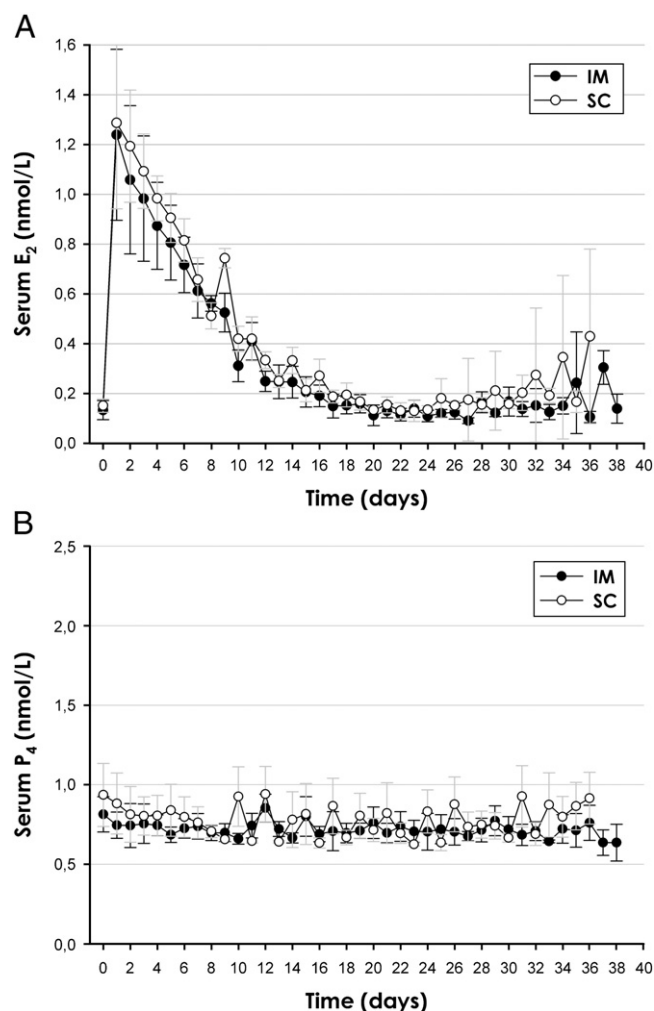


Fig. 1. (A). Estradiol serum concentrations (mean  $\pm$  SD) vs. time after SC or IM injection with MPA 25 mg +  $E_2$ -Cy 5 mg. (B). Progesterone serum concentrations (mean  $\pm$  SD) vs. time after SC or IM injection with MPA 25 mg +  $E_2$ -Cyp 5 mg.

levels remained consistently low ( $< 1.0$  nmol/L) in both groups throughout the 40-day posttreatment period (Fig. 1B).

Fig. 2 shows the comparative pharmacokinetic profiles adjusted to a one-compartment open model with first-order absorption and elimination. As can be observed, lower peak MPA levels were obtained after the SC than IM administration but did not represent a significant difference (Table 2). Furthermore, serum MPA levels were found to be higher by the end of treatment interval with the SC route.

A comparison was made of the mean values of the pharmacokinetic parameters between the IM and SC administration of MPA 25 mg +  $E_2$ -Cyp 5 mg (Table 2).

No statistical or clinical differences were observed for the means  $C_{max}$ ,  $T_{max}$  and AUC for serum MPA or serum  $E_2$ , nor for the  $T_{1/2abs}$  or  $t_{1/2el}$  for serum MPA.

No major adverse events were reported either locally or systemically. Forty-six common side effects, attributable to the use of the MPA plus  $E_2$ -Cyp contraceptive, were reported

Table 1  
Clinical characteristic of women by study group (mean  $\pm$  SD)

	IM	SC
Age (years)	33.5 $\pm$ 4.9	32.5 $\pm$ 6.4
Weight (kg)	64.1 $\pm$ 13.8	61.4 $\pm$ 7.4
Height (m)	1.60 $\pm$ 0.1	1.60 $\pm$ 0.1
BMI <sup>a</sup>	25.8 $\pm$ 3.8	25.6 $\pm$ 3.8
Pregnancies	1.9 $\pm$ 0.9	2.3 $\pm$ 1.1
Childbirths	1.2 $\pm$ 0.9	1.4 $\pm$ 1.5
Cesarean section	0.5 $\pm$ 0.6	0.7 $\pm$ 1.0
Abortions	0.2 $\pm$ 0.6	0.2 $\pm$ 0.4

<sup>a</sup> BMI was calculated as the individual's body weight divided by the square of her height (unit of measure of kg/m<sup>2</sup>).

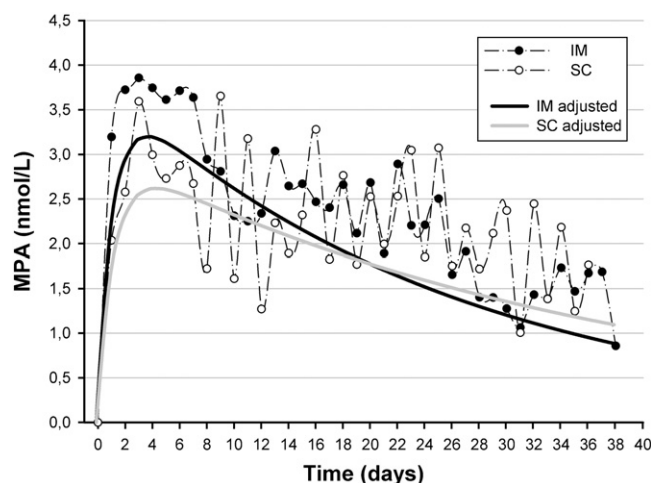


Fig. 2. Medroxyprogesterone serum concentrations (mean) vs. time after SC or IM injection with MPA 25 mg+E<sub>2</sub>-Cy 5 mg (dash lines) and the comparative pharmacokinetic profiles adjusted to a one-compartment open model with first-order absorption and elimination (solid lines).

by 21 women (11 from those who received the IM route of administration and 10 from those who received the SC route). These events were all minor and were similar to those reported in previous studies [15]. The most frequently observed were local pain (10% IM vs. 20% SC), headache (26% IM vs. 23% SC), breast tenderness (16% IM vs. 13% SC) and sick feeling (6% IM vs. 3% SC). Additionally, for IM, there were reports of acne (6%), asthenia (3%), emotional lability (3%) and dysmenorrhea (1%), and for SC, there were reports of allergy (3%), vaginal dryness (3%) and phosphenes (3%). In the present study, there were no statistically significant differences in the total or type of adverse events resulting from the use of this contraceptive (Fisher's Exact Test,  $p>.05$ ).

All women from both groups had withdrawal bleeding (defined as the first bleeding/spotting episode following injection). There was a similarity of the bleeding patterns in the IM and SC groups, a mean of 18 vs. 20 bleeding-free days, respectively ( $p<.05$ ), and also between these groups and the patterns observed in previous reports [15]. There was

a tendency to a slightly more regular bleeding and longer interval without bleeding after injection through the SC route. After the IM and SC injection, women experienced a mean of 4.4 vs. 3.8 bleeding days, respectively.

#### 4. Discussion

Combined injectable contraceptives, which contain progestin plus estrogen, were developed to address troublesome side effects of progestin-only formulations. With estrogen added to the long-acting progestin, bleeding cycles are more regular than they are with injectable progestin-only methods, and once-a-month, combined injectable contraceptives produce a more rapid return to fertility and prevent bone mineral density loss [16].

Early discontinuation criteria for reasons other than side effects or bleeding patterns included a poor acceptability of the requirement for frequent clinic visits. Women with proper guidance effectively self-administered their injection and consequently did not need frequent clinic attention [17,18]. Patient satisfaction with self-injection has been found to be high [19]. The SC route has other obvious advantages with respect to IM route, as it allows for more latitude in the qualifications necessary to administer medication, easier administration, greater privacy and less risk of local reactions (e.g., hematoma formation, intravascular injection and nerve injury) [19,20].

The advent of SC formulations for self-administration likely enhances the acceptability of contraceptives. A lower dose of a progestin-only injectable contraceptive DMPA (Depo-subQ Provera 104) was recently introduced. This SC formulation showed a slower rate of absorption and lower peak serum levels than IM DMPA given at the same interval [21]. There have been no published studies so far for subjects using self-injection of SC DMPA [20].

The present study addressed itself to evaluate differences in the pharmacokinetics from the combined monthly injectable MPA 25 mg+E<sub>2</sub>-Cyp 5 mg administered SC vs. IM. This hormonal contraceptive is administered as an aqueous suspension IM every 28–33 days within 5 days of onset of menstruation [22]. Presently, there is no formulation for specific SC administration.

No major differences were observed between either route of administration in relation to the main pharmacokinetic parameters ( $C_{max}$ ,  $T_{max}$ , AUC,  $T_{1/2abs}$  and  $t_{1/2el}$ ) of MPA and E<sub>2</sub>. The higher variation in serum E<sub>2</sub> levels at the end of treatment interval when using the SC than IM administration might reflect variations in follicular development.

The combined injectable formulation (MPA plus E<sub>2</sub>-Cyp) is a highly effective contraceptive administered by the IM route [1]. A previous report comparing DMPA administered by the IM and SC routes with particular focus on clinical efficacy and bone mineral density showed no significant differences between either routes of administration [9].

Table 2  
Pharmacokinetic parameters by study group (mean±SD)

Parameter	IM (n=14)	SC (n=15)	Unpaired <i>t</i> test
<b>MPA</b>			
$C_{max}$ (nmol/L)	4.69±1.52	3.83±1.56	0.17
$T_{max}$ (days)	4.75±2.09	6.52±2.07	0.45
AUC (day*nmol/L)	81.58±27.64	72.26±38.73	0.65
$T_{1/2abs}$ (days)	0.86±0.30	1.05±0.56	0.36
$t_{1/2el}$ (days)	24.03±21.74	30.90±15.11	0.42
<b>E<sub>2</sub></b>			
$C_{max}$ (nmol/L)	1.29±0.64	1.31±0.69	0.87
$T_{max}$ (days)	1.33±0.47	2.32±0.32	0.13
AUC (day*nmol/L)	12.46±3.59	14.57±3.70	0.13

Regarding women in the present study who were restricted to BMIs from 20 to 28 kg/m<sup>2</sup>, it is likely that this narrow range is not important for the results. Previous studies have shown no significant differences in pharmacokinetics of MPA between obese and thin/normal women receiving MPA and E<sub>2</sub>-Cyp [23,24]. Future studies should address the pharmacokinetics of this SC once-a-month combined injectable contraceptive in larger groups of women with different BMIs.

Little is known about the comparative pharmacokinetics and acceptability of combined injectable contraceptives. An SC route for DMPA has a lower rate of absorption than an IM route [25]. However, the efficacy and tolerability profile of the SC route is similar to that of the IM route of administration [21]. There is evidence supporting the bioequivalence of DMPA for the SC and IM routes of administration [9]. In the present study, it was demonstrated that there are no major differences observed with either route of administration of the combined injectable MPA plus E<sub>2</sub>-Cyp contraceptive. The duration of ovarian suppression and the other variables studied were similar in both groups. The only difference documented was a lower C<sub>max</sub> of MPA in the SC group, which did not reach statistical difference (p>.05). Overall, the present study confirms that the SC route of administration is as effective and safe as the IM route, with the advantage that it is suitable for self-administration and therefore might contribute to an increase in continuation rates for this injectable contraceptive.

Combined injectable contraceptives like MPA plus E<sub>2</sub>-Cyp also have the advantage of inducing a slightly more regular endometrial bleeding when employing the SC compared to the IM route of administration. Also, less infrequent bleeding patterns were found with the combined contraceptives than with progestin-only injectables, resulting in lower rates of early discontinuation due to amenorrhea or other bleeding problems [16]. In conclusion, this study demonstrates that the once-a-month combined injectable contraceptive MPA 25 mg plus E<sub>2</sub>-Cyp 5 mg administered by the SC route is effective for suppressing ovarian function, providing pharmacokinetic parameters and contraceptive efficacy comparable to those observed when the IM route of administration is employed. Future research should be directed to assessing the benefits of this SC contraceptive method that are related to its acceptability, and the possible variation in its effects when including a greater range of BMI.

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