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Dihydroxyprogesterone acetophenide 150 mg + estradiol enantate 10 mg as monthly injectable contraceptives

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Abstract

A survey among users and health personnel participating in the Salvadorian Social Security Institute (ISSS) Family Planning Program revealed interest in including a monthly preparation for injection as a contraceptive method offered by this Institution. The formulation containing dihydroxyprogesterone acetophenide (DHPA) 150 mg + estradiol enantate (E2EN) 10 mg was chosen for conducting an open and prospective study of efficacy and tolerability. Between January 1992 and March 1994, 7054 women were treated with this product for a total of 60 010 months.

A sample composed of 4505 women treated at this Institution confirmed that average users are young, have one or two children, do not show a particular geographical distribution and choose the monthly injection instead of oral contraceptives as the first contraceptive method or for the puerperium.

The study formulation showed a high efficacy (Pearl Index: 0.018) and tolerability (general withdrawal rate throughout the study: 27.09%). The most frequent adverse events included bleeding disorders, headache and mastalgia; their incidence decreased spontaneously from the sixth month (3.9%), reaching 0% after two years. Treatment was discontinued due to adverse events in 3.47%

of women. No significant bodyweight or systolic and diastolic blood pressure alterations were observed. Based on these results, the monthly injectable contraceptive was included in the basic product list at ISSS.

Introduction

About 166 000 women of child bearing age attend the Salvadorian Social Security Institute (ISSS), accounting for 22% of all Salvadorian women of child-bearing age. Thirty-five centers throughout the country offer a Reproductive Health Program including maternal care, child care and family planning services.

Family planning services consist of various alternative methods such as female and male sterilization, oral contraceptives, intrauterine devices, condoms, spermicidal agents, etc. In 1991, monthly injectable contraceptives were not included among these methods, but a survey conducted that year among users and health personnel revealed that many women desired this option or had adopted it from the private sector. Supported by reappearance of this contraceptive method at the worldwide level [1–3], it was therefore decided to assess its inclusion among family planning programs offered by the ISSS. A study evaluating the efficacy and side-effects of dihydroxyprogesterone acetophenide (DHPA) 150 mg + estradiol enantate (E2EN) 10 mg for injection, the most widely used formulation in our environment, was therefore undertaken to decide whether this option should be included or not in the ISSS's basic product list.

DHPA is a known progestogen agent. In the early 1960s, Lerner et al. showed that it maintained pregnancy in ovariectomized rats, without exerting virilizing effects on female fetuses [4]. At the experimental level, its activity is 2–5 times more powerful than that of progesterone [5,6]. In 1964, Taymor et al. [7] showed that it is capable of inhibiting ovulation in women, either alone or combined with E2EN. These authors concluded that the combination of DHPA and E2EN results in cyclic bleedings similar to those seen during normal ovulatory cycles. Reifenstein et al. and Rizkallah et al. [8,9] concluded later that the dosage level which results in bleedings most similar to physiological bleedings is DHPA 150 mg + E2EN 10 mg through the intramuscular route, applied between the 7th and 10th day of the menstrual cycle. Many other investigators assessed this formulation subsequently and confirmed its high contraceptive efficacy and its low incidence of side-effects [10–12].

In 1973, Sammour et al. [13] reported that, in some cases, the administration of this drug for three years slightly increased plasma protein levels, which reverted after treatment was discontinued. These authors concluded that the drug should be avoided in women with kidney disorders, but that it is well tolerated by healthy women with normal kidney function. Kidney function abnormalities were not reported by other investigators conducting studies with a 5-, 7- and 10-year duration [14–16].

In 1980, Rustrian [16] published his observations on 8074 cycles in 100 women, half of whom were treated continuously for 10 years: a 100% efficacy was reported, cycle duration was 30 ± 4 days, menstruation duration ranged from 3 to 5 days,

abnormal bleeding was only reported in 2.1% of cycles and fertility was recovered 30 to 90 days after drug discontinuation.

After intramuscular administration, DHPA penetrates into fatty tissues, where it is gradually released into the blood; it is mostly eliminated through the biliary route. E2EN also exhibits lipophilic features; its plasma half life is 5.5 days and it is mostly eliminated through the renal route [17,18].

This 10 mg formulation, unlike other monthly preparations for injection containing 5 mg estradiol esters, has been associated with improved bleeding patterns [19]. Schiavon et al. [20] reported serum estrone increases in long-term users, but such increases reverted spontaneously as treatment was continued, so they may be considered as occasional or casual findings. On the other hand, a series of experimental studies conducted by Moguilevsky et al. [21] and Wiemeyer et al. [22–24] indicated that 10 mg E2EN does not accumulate in the body nor is it an excessive or harmful dosage level, and suggested that its potency would be similar to or lower than that of oral contraceptives containing 30 μg ethinyl estradiol (EE).

Garza Flores and Hall [25] reviewed studies indicating that the formulation containing DHPA 150 mg + E2EN 10 mg does not result in adrenal, thyroidal, hepatic and renal function alterations nor in effects on coagulation and blood components. Later, this same Garza Flores group [26] found no significant prolactin secretion alterations, while the Schiavon group [20] monitored ovulation return after treatment discontinuation. The Melo group [27,28] found no hemostatic and lipoprotein changes. Moreover, only this monthly formulation for injection has been submitted to epidemiological studies about cancer, but no correlation has been found between its use and cervical oncological disease [29].

This background, as well as clinical use of DHPA 150 mg + E2EN 10 mg in other countries for many years, supports our study and the choice of this formulation for injection.

This open and descriptive study was conducted from January 1, 1992 to March 31, 1994 on a total of 7054 women treated for 60 010 cycles. General preliminary results were announced at the SAC IX International Congress in Guatemala from March 7–10, 1995 [30].

More detailed findings in 4505 women are described below. The objectives of the study were:

a) to describe general features of the user population interested in using this contraceptive method;

b) to determine cycle and bleeding duration during a 24-month treatment;

c) to assess type and incidence of treatment-related adverse events;

d) to assess treatment influence on blood pressure and bodyweight;

e) to define treatment withdrawal rates and reasons; and

f) to confirm the drug's efficacy.

Materials and methods

From the ethical point of view, this study protocol was reviewed and approved by the appropriate Honorable Board of Directors committee of the ISSS. It was conducted in all health centers offering family planning services. Training was given to all medical personnel, nurses and social workers involved in the ISSS Reproductive Health Program throughout the country.

The study included women needing a highly effective and reversible contraceptive method. Their features were as follows: women with no age limit in whom a combined hormonal treatment was indicated, women granting their informed consent and willing to receive the first injection between the 7th and 10th day after the beginning of menstruation or 8 days after a post-abortion curettage or 30–40 days after delivery. Exclusion criteria included: pregnancy or suspected pregnancy, history or presence of cardiovascular or thromboembolic disease, active hepatic disease or abnormal hepatic function tests, diabetes mellitus, breast cancer or undiagnosed nodule, abnormal uterine hemorrhage without accurate diagnosis.

Regular clinical and gynecological examinations were scheduled for users at admission, at 40 days, and at 3, 6, 12, 18 and 24 months after starting treatment. All injections, through the deep intramuscular route in the gluteal region, were applied at health centers by nurses involved in the Family Planning Program. Users were interviewed by nurses to assure a correct administration date (7th to 10th day of cycle), and to record previous cycle features and possible adverse events occurring during that cycle. This interview allowed nurses to detect abnormal medical conditions.

Standard clinical report forms were assigned to each selected user so that the following could be recorded: demographic characteristics, data obtained from interviews by nurses at injection application, medical examination results, dates at which bleeding started and ended, dates of injection application, adverse events experienced during treatment and reasons for treatment withdrawal, when applicable. Data were processed in a personal computer through Atlanta CDC's EPIINFO program version 5.01.

Results

A total of 4505 women were evaluated in this study.

Slight differences seen in total figures indicated below for certain items are due to lacking data and did not lead to significant result alterations.

Demographic characteristics

User distribution among the various health centers in the country, which were grouped into 4 main regions, is shown in Table 1. Such a distribution is similar to that exhibited by the population attending at the ISSS, both of them showing a higher

Table 1. Users' distribution according to geographical region

Region	*Number of users*	*%*
Metropolitan region	2081	46.2
Central region	1415	31.4
Eastern region	257	5.7
Western region	752	16.7
Total	4505	100.0

Table 2. Users' distribution according to age

Years	*Number of users*	*%*	*Cumulative %*
15–19	387	8.6	8.6
20–24	1928	42.8	51.4
25–29	1550	34.4	85.8
30–34	590	13.1	98.9
35 or more	50	1.1	100.0
Total	4505	100.0	

concentration in the metropolitan area. Almost half of the women were covered by the social security (47.5%) while the remaining benefited from social security services (52.5%), which is also compatible with the general population.

Women's age at the beginning of the study is shown in Table 2. More than half were younger than 25 years old. Mean age was 24.76 years (SD: 4.16, range: 15–41 years).

User distribution according to number of previous pregnancies and children alive is shown in Table 3. The difference between mean number of pregnancies (1.78) and mean number of children alive (1.61) should correlate with losses due to abortion and child mortality.

When defining contraceptive methods used by women before starting the study (Figure 1), it was found that almost 20% of them did not use any method. It should be noted that almost one quarter relied on postpartum nursing, and that they agreed to participate in the study even after being informed that effects of this contraceptive method on milk production and newborns had not yet been sufficiently established (findings in this subgroup will be communicated through a special report). More than one quarter of participating women took advantage of this opportunity to discontinue oral contraceptives not because of the OC side-effects but because the women thought the monthly injection could be 'a more convenient and practical alternative'.

Table 3. Users' distribution according to number of previous pregnancies and children alive

No. of pregnancies	*n*	*%*	*Cumulative %*	*No. of children alive*	*n*	*%*	*Cumulative %*
0	225	5	5	0	275	6.1	6.1
1	1933	42.9	47.9	1	2104	46.7	52.8
2	1509	33.5	81.4	2	1572	34.9	87.7
3–5	784	17.4	98.8	3–5	513	11.4	99.1
>5	54	1.2	100.0	>5	41	0.9	100.0
Total	4505	100.0		Total	4505	100.0	

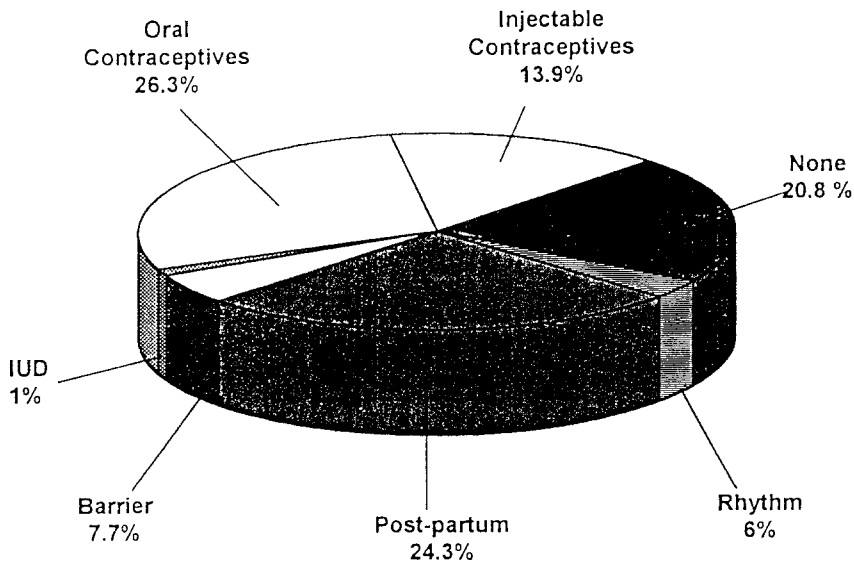

Figure 1. Distribution according to previous contraceptive method

Fourteen percent of women already used injectable contraceptives, the monthly injection the most frequently reported (9%).

The importance of these two latter groups is consistent with results obtained in the survey referred to in the introduction.

Finally, regarding users' educational level, 12% had not attended school; mean value was 8.6 years of school education and 60% had finished primary school; almost

Table 4. Cycle and bleeding duration during treatment

Months of treatment	*Cycle duration (Mean ± SD) (days)*	*Menstruation duration (Mean ± SD) (days)*
2	26.72 ± 6.32	5.38 ± 2.07
4	27.35 ± 5.65	5.41 ± 1.99
8	27.88 ± 4.76	5.44 ± 1.88
12	27.63 ± 7.36	5.39 ± 1.81
16	27.01 ± 6.72	5.22 ± 1.86
20	27.00 ± 7.87	4.93 ± 1.80
24	28.06 ± 6.63	4.94 ± 2.00

half (44.6%) had reached high school level. This is compatible with the educational level seen at the ISSS, which exceeds the mean value for El Salvador.

Cycle and bleeding duration

Cycle and bleeding duration during treatment is shown in Table 4. Pretreatment values for these parameters were altered because a significant percentage of users entered into the study with postpartum amenorrhea, so they were not considered as reliable indicators nor taken into account.

Although significant differences were not found, a trend towards shorter cycles at the beginning and towards slightly longer cycles as treatment continued was observed; notwithstanding, mean values were always within normal limits.

Regarding menstruation duration, a slightly inverse trend was observed; although not statistically significant and always within normal levels, menstruation tended to be shorter as treatment continued.

Treatment-related adverse effects

Discomfort, complaints or alterations reported by users were more frequent during the first months of treatment but decreased later, from the 6th month, reaching 0% at 2 years. The incidence of possible or probable study drug-related adverse events is shown in Table 5.

The most frequently reported adverse events were bleeding disorders (especially spotting and intermenstrual bleeding), headache and mastalgia.

Table 5. Incidence of treatment-related adverse events

	Month 1 (%)	*Month 6 (%)*	*Month 12 (%)*	*Month 18 (%)*	*Month 24 (%)*
Cycle <20 days	0	0	0.3	0	0
Cycle >36 days	0.9	0.3	0.6	0.7	0
Intermenstrual bleeding	0.1	1.8	0.9	0.7	0
Intermenstrual spotting	0	1.4	0.2	0.7	0
Amenorrhea	0	0	0	0	0
Mastalgia	0	1	0	0	0
Headache	0	0.3	0	0	0

Table 6. Evolution of bodyweight and systolic and diastolic blood pressure (mean ± SD)

Control	*Bodyweight (pounds)*	*Systolic blood pressure (mmHg)*	*Diastolic blood pressure (mmHg)*
0 days	126.70 ± 21.70	107.14 ± 9.10	67.94 ± 8.12
40 days	127.97 ± 22.09	106.82 ± 10.25	67.78 ± 7.69
6 months	128.40 ± 22.23	106.32 ± 9.77	67.08 ± 7.38
12 months	128.76 ± 21.55	106.81 ± 10.15	66.74 ± 7.40
18 months	131.80 ± 23.85	105.68 ± 7.40	66.59 ± 6.59
24 months	130.80 ± 9.90	106.84 ± 10.03	71.05 ± 8.09

Blood pressure and bodyweight

No statistically significant bodyweight or systolic or diastolic blood pressure alterations were observed during treatment. Bodyweight and blood pressure values are shown in Table 6.

Withdrawal rates and reasons

General treatment withdrawal rate during the whole study period was 27.09%. Reasons for withdrawal, as reported by users, are listed in Table 7.

Unexplained unattendance comes first (11.4%), followed by amenorrhea (7.2%), which was a reason for withdrawal especially after the first injection and in a higher

Table 7. Reasons for treatment withdrawal

Cause (as reported by user)	*% of treated users*	*% of reasons for withdrawal*
Unattendance	11.40	42.08
Amenorrhea	7.20	26.58
Change of method	2.22	8.19
Sterilization	2.01	7.42
Cycle >36 days	1.52	5.61
Cycle <20 days	0.85	3.14
Desire for pregnancy	0.79	2.92
Intermenstrual spotting	0.67	2.47
Intermenstrual bleeding	0.25	0.92
Headache	0.15	0.55
Mastalgia	0.03	0.12
Total	27.09	100.00

percentage of patients in the group starting treatment after delivery. For users in these circumstances, lack of menstruation was deceiving, and led to discontinuation of this contraceptive method in some of them; however, this cannot be considered as a study drug side-effect.

Regarding users who changed their contraceptive method (2.2%), most of them had been previous users of oral contraceptives and returned to them because they preferred them. Another 2% of women used the formulation for injection as a transitional method while their decision to undergo sterilization was made.

Withdrawal due to cycle duration disorders accounts for 2.37%, while withdrawal due to intermenstrual bleeding or spotting accounts for 0.92%. When withdrawal due to headache and mastalgia is added (0.18%), total withdrawal rates for medical causes add up to 3.47%.

Contraceptive efficacy

Only one pregnancy was reported throughout the study; it occurred during the first month of treatment in one user who received the injection on the 10th day of the menstrual cycle. Pregnancy was confirmed through ultrasound and was considered as treatment failure. Delivery took place 39 weeks later, with no complications.

It should be noted that this pregnancy was the only one observed during treatment, not only among users described here, but among all users receiving this formulation for injection at the ISSS between January 1992 and March 1994. If the 60 010 injections applied are considered, a Pearl Index of 0.018 is obtained.

Discussion and conclusions

In our environment, women interested in and capable of receiving this monthly injectable contraceptive method are mostly young women, with a mean age of <25 years. It should be emphasized that teenagers account for an important part of these women (8.5%), which is consistent with the profile of women using injectable contraceptives described in former investigations [31].

In terms of geographical distribution, users are concentrated in the metropolitan area, as well as among the insured population receiving health services provided by ISSS. This is therefore different from that seen in other countries, where formulations for injection are preferred in rural areas.

Differences in terms of socio-cultural level were also observed versus former descriptions. Our mean user attended high school, while users from other countries seemed to have a lower educational level. In this sense, however, it should be noted that the cultural level seen at the ISSS is different from that of other Salvadorian groups.

Most women interested in this method are not multiparous; almost half of them have one child or none and more than 80% have up to 2 children, which correlates with the age features described above.

One quarter considered this method as convenient for their postpartum period. Another quarter, who used oral contraceptives, searched for a more convenient or practical alternative to oral contraceptives. Twenty percent selected the formulation for injection as their first contraceptive method. Nine percent had already adopted it from the private sector at the beginning of the study. This confirms the need shown by a previous survey of considering this method as an alternative desired by the population.

Also, we confirmed that, as described previously for monthly injectable contraceptives [32,33], the formulation composed of DHPA 150 mg + estradiol enantate 10 mg allows cycles similar to physiological ones. They are slightly shorter at the beginning of treatment and longer afterwards, but their mean duration ranges from 27 to 28 days. Likewise, withdrawal hemorrhage is similar to a normal menstruation of about 5 days.

Bleeding disorders constitute, however, the most frequent treatment-related adverse events. Qualitatively, our results are consistent with previous investigations [33]. Our study also confirmed that such disorders decrease spontaneously as treatment is continued [32]. Quantitatively, the incidence of bleeding disosrders found in this study was similar to that reported by Rustrian [16] and lower than that found by others [10–12]. Withdrawal rates due to adverse events were remarkably low; we believe that this was the result of a previous and effective advice received by users at health centers. Various authors have shown that women informed about possible variations in their bleeding patterns accept and tolerate them much easier than women who are surprised by the unexpected appearance of such changes [33]. The same applies to other side-effects such as headache or mastalgia.

General withdrawal rates were indeed low. When reasons for withdrawal were analyzed, a considerable number had no explanation since users just stopped

attending. Although a higher number of cases of this nature was not seen in this study versus other investigations, the fact that injections were given at health centers could have been a burden for our users. In fact, we found that some of them preferred to continue this contraceptive method externally because they did not have time to go for the injection. Regarding reasons defined for withdrawal, an interesting finding was the low percentage of withdrawals due to medical reasons. The importance of previous advice in this sense has been mentioned.

We also confirmed the absence of significant bodyweight and blood pressure alterations, as reported before by other authors [16,34,35].

Finally, and consistent with previous publications [10,12,33], this study confirmed again the high contraceptive efficacy of this formulation. As indicated before, only one pregnancy was reported in a user receiving the study drug on the 10th day of menstrual cycle; this occurred two months after starting the study. As a preventive action, day 10 was excluded from that moment from injection schedules, and the first injection was recommended on the 7th day only. No other pregnancy was reported after this standardization.

We conclude that the monthly injectable contraceptive containing DHPA 150 mg + E2EN 10 mg is an option desired by an important and representative group of women attended at the ISSS, and that it is highly effective and well tolerated by this group. Based on these results, the product was incorporated into this Institution's basic product list; it is now offered as an alternative for family planning, and the number of users of injectable contraceptives is increasing daily; the number of users of other contraceptive methods is decreasing. These results will promote future studies in different subgroups (i.e. teenagers, puerperal, and perimenopausal women) and in particular situations (i.e. nursing, postabortion, return to fertility in women discontinuing contraceptives to become pregnant, etc.) in order to support findings in this general population.

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Resumé

Une enquête auprès des utilisatrices et du personnel de santé participant au programme de planning familial ISSS a fait ressortir l'intérêt que suscitait l'inclusion d'une préparation administrée par injection une fois par mois en tant que méthode contraceptive offerte par cette institut. Le produit contenant 150 mg d'acétophénide de dihydroxyprogestérone (DHPA) + 10 mg d'énanthate d'oestradiol (E_2EN) a été choisi pour mener une étude ouverte et prospective en vue de déterminer dans quelle mesure il était efficace et tolérable. Entre janvier 1992 et mars 1994, 7.054 femmes ont été traitées avec ce produit, correspondant à un total de 60.010 mois.

Constituées en groupe échantillon, 4.505 femmes ont fréquenté l'institut, nous permettant de confirmer qu'en moyenne les utilisatrices étaient jeunes, avaient un ou deux enfants, ne correspondaient pas à une distribution géographique particulière et choisissaient l'injection mensuelle comme première méthode contraceptive ou après la période puerpérale, de préférence aux contraceptifs oraux.

Le produit étudié s'est avéré hautement efficace (indice de Pearl 0,018) et tolérable (taux de retrait général pendant la durée de l'étude: 27,09%). Les effets négatifs les plus fréquents comprenaient des troubles de saignements, des céphalées et des mastalgies; ces troubles diminuaient spontanément à partir du sixième mois (3,9%), cessant totalement après deux ans. Le traitement a été abandonné par 3,47% des femmes à cause d'effets négatifs. Aucun changement significatif n'a été observé ni dans le poids corporel, ni dans la pression sanguine systolique et diastolique. Sur la base de ces résultats, le contraceptif mensuel injectable a été inclus dans la liste des produits de base de l'ISSS.

Resumen

Un estudio entre usuarias y personal de atención de la salud del Programa de Planificación Familiar ISSS indicó interés en incluir una preparación mensual inyectable como método anticonceptivo ofrecido por dicha institución. La formulación que contenía 150 mg de acetofenida de dihidroxiprogesterona (DHPA) y 10 mg de enantato de estradiol (E2EN) fue elegida para realizar un estudio prospectivo abierto sobre eficacia y tolerabilidad. Entre enero de 1992 y marzo de 1994, se trató a 7.054 mujeres con este producto durante un total de 60.010 meses.

Una muestra compuesta de 4.505 mujeres atendidas en dicho instituto permitió confirmar que las usuarias medias son jóvenes, tienen uno o más hijos, no señalan ninguna distribución geográfica en particular y eligen la inyección mensual en vez de los anticonceptivos orales como primer método anticonceptivo o para el puerperio.

La formulación estudiada registró una alta tasa de eficacia (Indice de Pearl: 0,018) y tolerabilidad (tasa general de interrupción durante el estudio: 27,09%). Los acontecimientos adversos más frecuentes comprendieron perturbaciones de sangrado, dolor de cabeza y mastalgia; su incidencia disminuyó espontáneamente a partir del sexto mes (3,9%), reduciéndose al 0% al cabo de dos años. El tratamiento fue abandonado debido a acontecimientos adversos por el 3,47% de las mujeres. No se observó ningún cambio significativo del peso corporal o de la tensión arterial sistólica o diastólica. En base a estos resultados, el anticonceptivo inyectable mensual se incluyó en la lista básica de productos del ISSS.