

Review Article

MEDROXYPROGESTERON ACETATE - A HORMONAL CONTRACEPTIVE

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ABSTRACT

Hormonal contraception refers to birth control methods that act on the endocrine system. Almost all methods are composed of steroid hormones, although in India one selective estrogen receptor modulator is marketed as a contraceptive. In the ensuing decades many other delivery methods have been developed, although the oral and injectable methods are by far the most popular. Progestogen-only contraceptives are available as injections, implants, oral preparations, hormone-releasing intrauterine devices and emergency contraceptives. These compounds can be used by women who are breast feeding or have other contra-indications to oestrogen therapy. The progestogens that are or have been used in 'progestogen-only' contraceptives are chlormadinone acetate, desogestrel, ethynodiol diacetate, levonorgestrel, lynoestrenol, medroxyprogesterone acetate (MPA), norethisterone, norethisterone acetate, norethisterone oenanthate, norgestrel, norgestrienone and progesterone. Of these, MPA, norethisterone oenanthate and progesterone are used only in this way; the remaining progestogens are also used in combination with oestrogens.

Key words: Progestogen, Contraceptive, Medroxyprogesterone acetate (MPA)

INTRODUCTION

Hormonal contraceptives are nearly 100% effective with perfect use; however, typical failure rates in the range of 3% to 9% reflect the fact that adherence with daily, weekly, monthly, or even tri-monthly regimens is a problem. ^[1, 2] Women commonly fail to take hormonal contraception as directed. Up to 60% of COC (combined oral contraceptive) users report irregular COC use, including missing pills or starting new pill packages late. ^[3]

In one survey conducted in 10 countries, nearly 75% of pill users forgot to take their daily pill when at home, and more than 25% said that they were more likely to forget to take their pill when on holiday. ^[4] In order to avoid the situation parental administration of progesterone is highly desirable. Medroxyprogesterone acetate (MPA) - only' contraceptives are available as injectable suspension preparations.

HISTORICAL OVERVIEW

The hormonal action of progesterone was discovered in 1929, following that of estrogen in 1923.^[5] By 1931–1932, nearly pure crystalline material of high progestational activity had been isolated from the corpus luteum of animals, and by 1934, pure crystalline progesterone had been refined and obtained and the chemical structure of progesterone was determined by professor Adolf Butenandt at the Chemisches Institute of Technical University in Gdańsk, who extracted this new compound from several thousand liters of urine.^[5]

Chemical synthesis of progesterone from stigmasterol and pregnanediol was accomplished later that year. Up to this point, progesterone, known generically as corpus luteum hormone, had been being referred to by several groups by different names, including corporin, lutein, luteosterone, and progestin.^[5] In 1935, at the time of the Second International Conference on the Standardization of Sex Hormones in London, England, a compromise was made between the groups and the name progesterone (progestational steroidal ketone) was created.^[5] Shortly following its chemical synthesis, progesterone began being tested clinically in women. In 1934, Schering introduced progesterone, along with estradiol (brand name Progyon) and testosterone (brand names Testoviron, Proviron), as a pharmaceutical drug, under the brand name Proluton. It was originally administered by intramuscular injection because it is rapidly inactivated after oral ingestion.

The development of injectable progestogen-only contraceptives resulted from a growing understanding of steroid hormones and from the research that eventually led to the development of combined oral contraceptives. In 1953, Karl Junkman and colleagues synthesized the first injectable progestogens and then developed the first injectable contraceptive, norethisterone oenanthate, in 1957. This compound is now approved for contraceptive use in over 60 countries. MPA was synthesized in the late 1950s, and its depot form was subjected to clinical trials in 1963, before being released onto the international market. It has been approved for use as a contraceptive in a steadily increasing number of countries over the last 30 years and is now available in over 100 countries worldwide. Concern about an association with cancers of the breast, endometrium and cervix and other possible side-effects meant that depot MPA was approved as a contraceptive in the United States only in 1992, some 25 years after the manufacturer's first application however, it had already been approved for the treatment of conditions such as endometrial cancer, and legislation in the United States does not prohibit the use of approved drugs for non approved indications.^[6] Nevertheless, there are still concerns in the international community about issues of informed consent for the use of these long-acting methods and the potential abuse of their administration to poorly educated groups.^[7] Although the very first oral contraceptive, which was tested in Puerto Rico in 1955, contained only norethynodrel and was, technically speaking, a progestogen-only oral contraceptive it was superseded by the combination of mestranol and norethynodrel during development, as the combination was shown to prevent ovulation consistently.^[8] Progestogen-only oral contraceptives were developed in response to concern raised in the late 1960s about the side-effects of oestrogens in combined oral contraceptives. The prototype progestogen-only oral contraceptive contained chlormadinone acetate and was introduced in 1969. It was withdrawn in 1970 because of evidence that it induced breast nodules in laboratory animals. Other progestogen-only oral contraceptives were developed subsequently, containing progestogens of the norethisterone and levonorgestrel groups.^[7]

Subcutaneous progestogen implants were developed in the late 1960s and 1970s and were approved in Finland in 1983, in Sweden in 1985, the Dominican Republic, Ecuador, Indonesia and Thailand in 1986, China, Colombia, Peru and Venezuela in 1987, Chile and Sri Lanka in 1988 and the United States in 1990.^[9]

A device that releases progesterone into the uterus was developed in the early 1970s and has been available since 1976. This had the disadvantage of a high rate of hormone release, necessitating annual replacement.^[7] An intrauterine device that releases effective concentrations of levonorgestrel over a five-year period was approved in Finland in 1990 and in Sweden in 1992 it has since been approved in Belgium, Denmark, France, Iceland, Norway, Singapore, Switzerland and the United Kingdom.^[10,11]

INJECTABLE PROGESTOGENS

MPA a better injectable contraceptive is available worldwide, and its formulation DEPO-PROVERA has remained unchanged since its development in the late 1950s and early 1960s. MPA is administered in an aqueous microcrystalline suspension by deep intramuscular injection into the gluteal or deltoid muscle. This depot results in a high plasma concentration of MPA initially, which declines exponentially thereafter. It is given at a dose of 150 mg every 90 days or three months.^[6] Menstrual disturbances are common in women using these compounds and may take the form of amenorrhoea or frequent and/or irregular bleeding. Weight gain is also a common side-effect.

MECHANISM OF ACTION

MPA inhibit follicular development and prevent ovulation as a primary mechanism of action.^[12] Negative feedback decreases the pulse frequency of gonadotropin-releasing hormone (GnRH) release by the hypothalamus, which decreases the release of follicle-stimulating hormone (FSH) and greatly decreases the release of luteinizing hormone (LH) by the anterior pituitary. Decreased levels of follicular stimulating hormone (FSH) inhibit follicular development, preventing an increase in estradiol levels. The negative feedback and the lack of estrogen positive feedback on LH release prevent a mid-cycle LH surge. Inhibition of follicular development and the absence of a LH surge prevent ovulation.^[12]

Another primary mechanism of action of all progestogen-containing contraceptives is inhibition of sperm penetration through the cervix into the upper genital tract (uterus and fallopian tubes) by decreasing the amount of and increasing the viscosity of the cervical mucus.^[12]

CLINICAL PARTICULARS

The brand name DEPO-PROVERA (medroxyprogesterone acetate) contraceptive (Fig.1) Injection is indicated only for the prevention of pregnancy. To ensure that DEPO-PROVERA contraceptive Injection is not administered inadvertently to a pregnant woman, the first injection must be given only during the first 5 days of a normal menstrual period; only within the first 5-days postpartum if not breast-feeding, and if exclusively breast-feeding, only at the sixth postpartum week. It is a long-term injectable contraceptive in women when administered at 3-month (13-week) intervals. Dosage does not need to be adjusted for body weight. In five clinical studies using DEPO-PROVERA contraceptive Injection, the 12-month failure rate for the group of women treated with DEPO-PROVERA contraceptive Injection was zero (no pregnancies reported). The effectiveness of DEPO-PROVERA contraceptive Injection is dependent on the

patient returning every 3 months (13 weeks) for reinjection. In case of children MPA is not indicated before menarche. [6]



Fig.1: DEPO-PROVERA INJECTION- A: Medroxyprogesterone acetate 150 mg/ml and B: Medroxyprogesterone acetate 400 mg/ml

Posology and Method of administration

Each mL contains injectable suspension of MPA 150 mg. Injectable suspensions should be shaken well before used to ensure that the dose being administered represents a uniform suspension. The recommended dose is 150 mg of MPA Injectable suspension every 12-13 weeks (3 months) administered by intramuscular (i.m) injection in the gluteal or deltoid muscle. The i.m. suspension is not formulated for subcutaneous injection. The initial i.m. injection should be given during the first 5 days after the onset of normal menstrual period; within 5 days post partum if not breast feeding or, if exclusively breast-feeding, at or after 6 weeks postpartum. If the time interval between the i.m. injections is greater than 13 weeks, pregnancy should be ruled

out before administrating the next i.m. injection. No clinical studies have evaluated the effect of hepatic diseases and renal diseases.

Contraindications ^[13, 14]

- Current breast cancer (within the previous five years).
- Gestational trophoblastic neoplasia with abnormal human chorionic gonadotrophin (hCG) level.
- Current severe impairment of liver function or history of liver adenoma or steroid-induced cholestatic jaundice.
- History of severe arterial disease or very high risk factors - risk of thrombosis and arterial disease may be increased.
- Acute porphyria, even if there is no history of active disease.
- Pregnancy - this should be excluded before injection (a history of recent normal menstruation is adequate).
- Unexplained vaginal bleeding.

Special precaution for use

- Cardiovascular disorders like coronary artery diseases and stroke.
- Ovarian Cancer.
- The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests.
- Patients who have a history of psychic depression should be carefully observed and the drug not be re-administered if the depression recurs.
- Patients should be counselled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Drug interaction

Aminoglutethimide administered concomitantly with high dose of oral MPA may significantly depress the serum concentration of MPA.

Pregnancy and Lactation

Health-care providers should be alert to the possibility of an ectopic pregnancy among women using MPA contraceptive Injection who become pregnant or complain of severe abdominal pain. Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA C-contraceptive injection. In nursing mothers treated with DEPO-PROVERA Contraceptive Injection, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

PHARMACOKINETICS

Oral administration

The route of administration impacts the effects of progesterone. Oral MedroxyProgesterone (OMP) has a wide inter-individual variability in absorption and bioavailability. In contrast, progestins are rapidly absorbed with a longer half-life than progesterone and maintain stable

levels in the blood. The absorption and bioavailability of OMP is increased approximately two-fold when it is taken with food. Progesterone has a relatively short half-life in the body. As such, OMP is usually prescribed for twice or thrice-daily administration or once-daily administration when taken by injection.^[15] Via the oral route, peak concentrations are seen about 2–3 hours after ingestion, and the half-life is about 16–18 hours.^[15] Significantly elevated serum levels of progesterone are maintained for about 12 hours, and levels do not return to baseline until at least 24 hours have passed.^[15] OMP is prescribed in divided doses. Progesterone, when taken orally, undergoes gastrointestinal (especially hepatic) metabolism to form hydroxylated metabolites, which in turn are metabolized into sulfate and glucuronide derivatives. Enzymes involved in the hepatic metabolism of progesterone include, particularly, CYP2C19 and CYP3A4, as well as CYP2C9.^[16,17]

Intramuscular injection

With intramuscular injection of 10 mg progesterone suspended in vegetable oil, maximum plasma concentrations (C_{max}) are reached at approximately 8 hours after administration, and serum levels remain above baseline for about 24 hours.^[18] Doses of 10 mg, 25 mg, and 50 mg via intramuscular injection result in mean maximum serum concentrations of 7 ng/mL, 28 ng/mL, and 50 ng/mL, respectively.^[18] With intramuscular injection, a dose of 25 mg results in normal luteal phase serum levels of progesterone within 8 hours, and a 100 mg dose produce mid-pregnancy levels. At these doses, serum levels of progesterone remain elevated above baseline for at least 48 hours, with a half-life of about 22 hours.^[19] Due to the high concentrations achieved, progesterone by intramuscular injection at the usual clinical dose range is able to suppress gonadotropin secretion from the pituitary gland, demonstrating anti-gonadotropic efficacy (and therefore suppression of gonadal sex steroid production).^[18]

Subcutaneous injection

MPA can also be administered alternatively via subcutaneous injection, with the new aqueous formulation Prolutexin Europe being intended specifically for once-daily administration by this route.^[19] This formulation is rapidly absorbed and has been found to result in higher serum peak progesterone levels relative to intramuscular oil formulations. In addition, subcutaneous injection of progesterone is considered to be easier, safer (less risk of injection site reactions), and less painful relative to intramuscular injection. The terminal half-life of this formulation is 13 to 18 hours, which is similar to the terminal half-lives of OMP and intramuscular progesterone.^[19]

Clearance

MPA is metabolized mainly in the liver.^[18] It is reduced to a variety of active and inactive metabolites, including pregnanediol, pregnanetriol. These metabolites are subsequently conjugated into glucuronide and sulfate forms.^[18] In urine, pregnanediol glucuronide is the major metabolite of progesterone.^[5] It has been found to constitute about 30% of an injection of progesterone.^[5]

EPIDEMIOLOGY

In the National Statistics Opinions Survey of UK households, 3% of women aged 16-49 years said they used the MPA injection as their method of contraception.^[20] The percentage is higher (9-11%) amongst women attending community clinics and, having dipped between 2005 and 2011, its usage has returned to previous rates.^[18] The majority of these women are young - 18-19

years old. Depot contraceptives are available only for women in the UK, but trials of monthly testosterone injections for men have been undertaken in China.^[22]

FAILURE RATE

Provided that women return every 12 weeks for their injection, there is a very low failure rate in studies - around 2 per 1,000 women per year. However, data from the USA suggest the real-life failure rate is about 6 per 100 women per year; it is more effective than oral contraception, although it is not as effective as the intrauterine devices or contraceptive implant.^[23] Neither obesity nor the use of liver enzyme-inducing medication affects the failure rate of MPA. The efficacy of MPA is lowered by enzyme-inducing drugs. Broad-spectrum antibiotics do not affect the efficacy of either injectable.^[24]

UNDESIRABLE EFFECTS

Intramuscular (i.m.) formulations of MPA induce following undesirable effects (Table-1)

Table-1

Disorders	Event
Infection	Vaginitis
Immune system disorders	Hypersensitivity reactions (Anaphylaxis and angioedema)
Endocrine disorders	Prolonged anovulation
Metabolism and nutritional disorders	Fluid retention, weight change
Psychiatric disorders	Depression, Decreased libido, Insomnia and nervousness.
Nervous system disorders	Convulsion, Dizziness and Headache
Vascular disorders	Thromboembolic disorders
Gastro intestinal disorders	Abdominal pain or discomfort and Nausea.
Hepato-biliary disorders	Jaundice
Skin and subcutaneous tissue disorders	Acne, alopecia, Hirsutism and Rash
Reproductive system and breast disorders	Abnormal uterine bleeding, amenorrhea, pelvic pain and breast tenderness
Investigations	Decrease glucose tolerance, Disturbed liver function and loss of bone mineral density.

WARNINGS

Bleeding Irregularities

Most women using DEPO-PROVERA (MPA) Contraceptive Injection experience disruption of menstrual bleeding patterns. Altered menstrual bleeding patterns include irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding

persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology, and appropriate treatment should be instituted when necessary.

As women continue using DEPO-PROVERA(MPA) Contraceptive Injection, fewer experience irregular bleeding and more experience amenorrhea. By month 12 amenorrhea was reported by 55% of women, and by month 24 amenorrhea was reported by 68% of women using DEPO-PROVERA(MPA) Contraceptive Injection.^[25]

Bone Mineral Density Changes

Use of MPA Contraceptive Injection may be considered among the risk factors for development of osteoporosis. The rate of bone loss is greatest in the early years of use and then subsequently approaches the normal rate of age related fall.

Cancer Risks

Long-term case-controlled surveillance of users of DEPO-PROVERA (MPA) Contraceptive injection found slight or no increased overall risk of breast cancer and no overall increased risk of ovarian, liver, or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer in the population of users.^[26, 27, 28, 29, 30]

Thromboembolic Disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, the drug should not be re-administered.

Ocular Disorders

Medication should not be re-administered pending examination if there is a sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should not be re-administered.

Unexpected Pregnancies

To ensure that DEPO-PROVERA (MPA) Contraceptive Injection is not administered inadvertently to a pregnant woman, the first injection must be given only during the first 5 days of a normal menstrual period; only within the first 5-days postpartum if not breast-feeding, and if exclusively breast-feeding, only at the sixth postpartum week. Neonates from unexpected pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA (MPA) Contraceptive Injection may be at an increased risk of low birth weight, which, in turn, is associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.^[31, 32]

CONCLUSION

In conclusion, If 100 sexually active women don't use any contraception, 80 to 90 will become pregnant in a year. Contraceptive injections are over 99 per cent effective. This means less than four women in every 1,000 will get pregnant over two years. The MPA injection is a method of long-acting reversible contraception (LARC). All LARC is very effective because while it is being used you do not have to remember to take or use contraception. MPA are injected into a muscle, usually in your buttocks MPA can also sometimes be given in the arm. Women will need to have injections every 13 weeks if you have MPA injection. Women do not need to have a vaginal examination or a cervical screening test to have a contraceptive injection. Most women can have a contraceptive injection. Your doctor or nurse will need to ask you about your own and your family's medical history to make sure a contraceptive injection is suitable. Do mention any illness or operations you have had. Some of the conditions which may mean you should not use

the injection if you think you might already be pregnant, you do not want your periods to change or you want a baby within the next year.

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