A comparison of progestogen-only injectable contraceptives

Adams BDP, MSc(Nursing), Sexual and Reproductive Health Nurse Practitioner, Pinelands Business Park, Ndabei, Cape Town

Correspondence to: Bridget Adams, e-mail: badams@quinhealth.co.za

Keywords: progestogen-only injectable contraceptives, POICs, DMPA, NET-EN, Petogen®, Depo-Provera®, Nur-Isterate®

Abstract

Progestogen-only injectable contraceptives (POICs) are slow-release reversible preparations that last for 2-3 months. Two are available in South Africa, namely depot medroxyprogesterone acetate (DMPA), marketed as Petogen® and Depo-Provera®, and norethisterone enantate (NET-EN), marketed as Nur-Isterate®. They provide safe, convenient and acceptable contraception with high use-effectiveness. An overview of the similarities and differences between DMPA and NET-EN are outlined in order for practitioners to assist women in the selection of an acceptable POIC. Particular information on bleeding profiles, managing overdue injections and controlling breakthrough bleeding is outlined. Recommendations are given for adolescents and older women. The POIC effects on certain diseases are discussed.

Introduction

Progestogen-only injectable contraceptives (POICs) are slow-release reversible preparations that last for 2-3 months. Two are available in South Africa, namely depot medroxyprogesterone acetate (DMPA), marketed as Petogen® and Depo-Provera®, and norethisterone enantate (NET-EN), marketed as Nur-Isterate®. They provide safe, convenient and acceptable contraception with high use-effectiveness.

Contraceptive mechanism of action

DMPA and ENT-EN work in three ways:

- They inhibit ovulation by suppressing the levels of lutenising hormone (LH) and follicle-stimulating hormone (FSH)
- Increased viscosity of the cervical mucus impairs the movement of sperm into the uterine cavity
- The endometrial lining becomes thin and unsuitable for implantation.1,2

Depot medroxyprogesterone acetate

The pharmacological composition of DMPA is medroxyprogesterone acetate, a semi-synthetic derivative of progesterone that features the same pharmacological profile, but is remarkably more potent.

DMPA inhibits gonadotropin-releasing hormone pulsatility and gonadotropin secretion, and the LH is much more suppressed than the FSH, thereby effectively preventing ovulation. This results in the oestradiol levels being low in long-term users.

DMPA greatly alters the endometrial lining which impacts upon bleeding patterns.2,3 Duration of action is 12 weeks. Minimal follicular activity occurs towards the end of the injection period, which may result in breakthrough bleeding.1

Norethisterone enantate

The pharmacological composition of NET-EN is a progestogen structure in an oily solution. The moderate suppression of FSH and LH occurs, and there are effective alterations in the cervical mucus.4 Duration of action is eight weeks.

Metabolic processes

Both DMPA and NET-EN are metabolised in the liver, and excreted in the urine.2

Depot medroxyprogesterone acetate

Maximum blood levels are reached 5-10 days after administration with DMPA. The blood level is controlled by the absorption rate of the micro crystals at the injection site.
Women’s Health: A comparison of progestogen-only injectable contraceptives

Norethisterone enantate

Maximum blood levels are reached seven days after the administration of NET-EN. The hormone is absorbed from the injection site and transported to the liver. It is metabolised and stored in the fatty tissue and gradually released.

Effectiveness

Both are safe for long-term reversible contraception, and are almost 99% safe if used correctly. Determination of the level of effectiveness takes into account all users, i.e. those who use it without error and those who are careless.\(^5\)

Depot medroxyprogesterone acetate

DMPA is highly reliable, with a failure rate of < 0.5%.\(^2\) This is the percentage expressed using the life table method, i.e. the number of pregnancies per 100 users, expressed as a percentage after the use of a method for one or more years.\(^3\)

Norethisterone enantate

NET-EN is reliable, with a failure rate of < 1%.

Administration

The commencement of progestogen-only injectable contraceptives

Ideally, both POICs should be started within five days of the menstrual cycle, to rule out pregnancy. Injection in the first seven days of menses results in immediate ovulation suppression. However, POICs can be commenced at any stage of the menstrual cycle, providing that the woman is not pregnant. The quick start method means that she does not have to wait for her next menses to begin. The 14-day rule should be observed, which means that she must abstain from, or have protected sexual intercourse, for 14 days after the administration of the injection if started in mid cycle.\(^3\)

Depot medroxyprogesterone acetate

The dosage of 150 mg/ml of DMPA should be taken every 12 weeks, or 1 ml intramuscularly. The dosage does not need to be adjusted for body weight.

Norethisterone enantate

The dosage of 200 mg/ml of NET-EN should be taken every eight weeks, i.e. 1 ml intramuscularly. The ampoule must be warmed to body temperature to facilitate easier withdrawal of the syringe. Afterwards, the site of injection must be covered with a plaster to prevent the partial reflux of the solution.\(^6\)

Injection technique

A deep intramuscular injection should be given, using the gluteus muscle. If the woman’s body mass index (BMI) is above 35 kg/m\(^2\), it should be administered into the deltoid muscle. The “Z” injection technique pattern is advised for obese women.\(^1\) The injection site must not be massaged as this increases the rate of absorption. Injectable contraceptives should be administered with a Promex® syringe. The Smart Lock® syringe is unsuitable as some of the solution remains in the syringe and thus a lesser dose is given.\(^6\)

Post-miscarriage or termination of pregnancy

Both POICs can be given within seven days of the event.

Postpartum

The POICs are best given six weeks postpartum, but may be given immediately after delivery, and have no effect on lactation.\(^1,2\)

Management of overdue injections

Depot medroxyprogesterone acetate

The DMPA injection may be given up to four weeks late. If the time period is longer than four weeks, a pregnancy test should be conducted and the injection administered if the test is negative.\(^4\)

Norethisterone enantate

The NET-EN injection may be given up to two weeks late. If the time period is longer than two weeks, a pregnancy test should be conducted and the injection administered if the test is negative.\(^3\)

Depot medroxyprogesterone acetate and norethisterone enantate

Women should follow the 14-day rule. A note should be made in the patient records to conduct a pregnancy test at the next visit. Significant risks to the foetus have not been found if the POICs are given inadvertently if the patient is pregnant.\(^4,7\) Follow-up injections may be given one week early for convenience, or to relieve breakthrough bleeding.\(^4\)

Contraindications for both types of progestogen-only injectable contraceptives

Absolute contraindications [World Health Organization (WHO) Category 4: Do not use] include:

- Undiagnosed vaginal bleeding
- Hepatic disease and abnormal liver function tests, but POICs can be used in the post hepatitis B carrier state.
- Current breast cancer
Women's Health: A comparison of progestogen-only injectable contraceptives

- **Uncontrolled hypertension**: POICs have no effect on blood pressure, but the package insert states that hypertension is contraindicated.⁷
- **Porphyria**
- **Allergy to Progestogens.**¹²,⁴,⁷

Relative contraindications (WHO Category 3: Risks of use may exceed benefits) include:
- Not for short-term contraception
- Hypo-oestroginism symptoms, such as osteoporosis and hot flushes
- Lipid abnormalities
- Recent thromboplastic disease, arterial disease, ischemic heart disease or a stroke⁷
- Anorexia or a weight below 45 kg (or BMI below 17 kg/m²), as the medicine is injected into the muscle and stored and released from the fatty tissue
- Patients with diabetes mellitus should be carefully supervised
- Cultural or religious taboos regarding menstrual irregularities.

### Side-effects

The most common side effects of both POICs are:
- Changes in menstrual patterns that may result in amenorrhea and breakthrough bleeding
- Weight gain
- Headaches
- A delay in ovulation when discontinued, thus a delay in return to fertility
- Mildly androgenic effects may increase existing depression, acne and hair loss.

One third of users discontinue taking POICs during the first year because of the side-effects.¹⁴,⁹

#### Norethisterone enantate

The side-effects of NET-EN are not as pronounced as those experiencing when using DMPA. There is less breakthrough bleeding, headaches and androgenic effect. It does not appear to have similar weight gain effects, and there is little evidence of BMD loss in adolescents, and a minimal effect is noted in older women.⁵,¹⁰

#### Bleeding profile

Changes in the menstrual cycle are inevitable with injectable contraceptives, and are commonly referred to as “menstrual chaos". Withdrawal bleeding may be heavy, irregular or absent, and there may be spotting. Amenorrhea is a predictable side-effect of DMPA and NET-EN owing to the inhibition of both ovulation and follicular development. Amenorrhea may be generally more acceptable to women than prolonged or frequent bleeding.²

Many women consider regular menses as fertility and pregnancy indicators, and associate irregular menstrual patterns with ill health. Furthermore, menstrual patterns have sexual, socio-cultural, economic and sometimes religious implications, which make it an important factor that affects women's lives. It is not surprising that women do not easily tolerate disruption to their menstrual patterns, and that menstrual disturbances are the main side-effect that women cite as the reason for discontinuing the use of injectable contraceptives.¹³,⁷

#### Depot medroxyprogesterone acetate

Menstrual chaos is frequent at first with DMPA, but amenorrhea is common after approximately one year of use. There may be an increase in spotting towards the end of the injection period. Persistent default or late injections commonly cause menstrual chaos which is difficult to control.

#### Norethisterone enantate

There is sufficient follicular activity for adequate oestrodial levels in many women on NET-EN, and they may have regular menses.¹,² There appears to be less menstrual chaos and less amenorrhoea, when compared to the use of DMPA.

It is very important to advise women about the changes to their menses prior to commencing the injectable contraceptive method, and to counsel for endurance if breakthrough bleeding occurs before the treatment commences. Another method should be used if a lack of menses is unacceptable.

#### Return to fertility

There is a relatively extended return to fertility with both POICs, when likened to oral contraceptives or intrauterine devices (IUD) or subdermal implants.
When DMPA and NET-EN have been compared in the same population, with a common method of detecting ovulation, NET-EN had a comparatively shorter time for the return of ovulation, relative to DMPA.\(^{1,3,11,12}\)

Time to ovulation post injection ranges from:
- 5–24 weeks: NET-EN
- 5–49 weeks: DMPA\(^{10,12}\)

**Drug interactions**

Drug interactions include concomitant chronic steroid use, owing to additional risk factors for a low BMD.\(^3\) There is a possibility of bleeding at the injection site in warfarin users.

**Depot medroxyprogesterone acetate**

Reduced contraceptive efficacy has not been observed with use of antiretroviral drugs (ARVs), rifampicin and enzyme-inducing anticonvulsant drugs. There is no evidence that DMPA injection intervals should be reduced.\(^{1,3,6,7,9,13,14}\)

**Norethisterone enantate**

Contraceptive efficacy using NET-EN may be reduced with concurrent use of:
- ARVs
- Some barbiturates
- Hydantoin anticonvulsant drugs
- Rifampicin.\(^3,4,13\)

It is recommended that NET-EN should be given at six-week intervals. However, this is costly. Thus, a change to DMPA is suggested.\(^6\)

**Benefits of both progestogen-only injectable contraceptives**

Both POICs are extremely effective (99%) provided that the injection is repeated at the correct intervals. They do not depend on a high level of user compliance, and the forgetfulness associated with the oral methods is minimised.

There are beneficial social effects too as the method is under the control of the woman, is highly convenient, non-intercourse related and allows for contraception independent of sexual intercourse. The method is fully reversible with no loss of fertility. Lactation is not suppressed either. It is actually enhanced, owing to the increased production of prolactin. There is decreased bleeding. Therefore, it is beneficial in haemorrhagic anemia, and has some haemopoietic effect. POICs are safer than combined oral contraceptives as there are no oestrogen-related side-effects, and thus no increased risk of deep vein thrombosis, pulmonary embolism, a stroke or myocardial infarction.

This method mainly benefits women who are unable to take oestrogen, or those aged 35 years and older who smoke.

**Disadvantages of both the progestogen-only injectable contraceptives**

The effects cannot be reversed once administered, so women who suffer the side-effects need to endure them for the duration of action of the contraceptive. POICs should not be the choice of contraception if a pregnancy is planned by women in their late 30s to early 40s.

**Age-specific information**

Both POICs are safe for long-term use in women of all ages.

**Adolescents**

The WHO recommends that the advantages of DMPA use in adolescents generally outweigh theoretical concerns about fracture risk.\(^7\) NET-EN may cause less menstrual disturbance, and be more acceptable in young women, or any women who prefer the possibility of more regular menses. Studies have shown that adolescent users are concerned about menstrual chaos or amenorrhoea, and that irregular menses are perceived to be indicative of disease. Most adolescents discontinued the method for that reason.\(^2,3,7\) There is evidence that adolescent users are more likely to gain weight, particularly if the woman is obese prior to commencing the POIC, and specifically DMPA.\(^3,6\)

**Perimenopause**

Little or no difference in BMD has been found in studies on long-term DMPA users, including postmenopausal women. Thus, it is reasonable to assume that older women can use POICs. However, the WHO eligibility criteria maintain that women aged 45 years and older fall into category 2, owing to BMD risk.\(^1,3,7,15\)

POICs are not recommended in women aged 45 years and older with high cholesterol, owing to a possible detrimental effect on the lipid profile.\(^1\) Long-term use in older women may cause a hypoestrogenic state and possible menopause-like symptoms. Menopause may be masked owing to amenorrhoea. Some menopausal women request DMPA to alleviate the symptoms of menopause, such as hot flushes.

There is some evidence of efficacy of POICs decreasing menopausal vasomotor symptoms. However, it would be more beneficial for women to make lifestyle changes, i.e. increased exercise and the consumption of a diet that is high in calcium and vitamin D, and low in fat.\(^2,1\)

Women aged 45 years and older should be encouraged to discontinue injectable contraceptives, and to use
Women’s Health: A comparison of progestogen-only injectable contraceptives

progesterone-only pills or condoms, as injectable contraceptives are considered to be superfluous around the perimenopause.\(^1\)\(^,\)\(^10\)

The best practice is for women to make a contraceptive decision by the age 40, and to consider an IUD, subdermal implant or sterilisation.

**Disease-specific information**

DMPA and NET-EN have some effects on the following conditions.

**Endometrial cancer**

There is an 80% decreased risk of endometrial cancer with the use of POICs, thought to be owing to the direct antiproliferative effect of progestogen on the endometrium, and the indirect reduction in oestrogen levels through the suppression of ovarian follicular development.\(^1\)\(^,\)\(^3\)\(^,\)\(^12\)\(^,\)\(^17\)

**Ectopic pregnancies**

POICs reduce the risk of ectopic pregnancies and functional ovarian cysts (no ovulation).\(^1\)\(^,\)\(^3\)

**Fibroids and endometriosis**

Possible reduction if amenorrhea is achieved.\(^1\)\(^,\)\(^2\)\(^,\)\(^7\)

**Ovarian cancer**

There is no epidemiological evidence of association between DMPA use and the risk of ovarian cancer.\(^3\)\(^,\)\(^6\)

**Premenstrual tension**

There is a decreased incidence of primary dysmenorrhea, premenstrual tension and ovulation pain with the use of POICs.\(^7\)\(^,\)\(^14\)

**Sickle cell disease**

DMPA is the method of choice in sickle cell disease as it helps to prevent the painful sickling crisis that occurs when the red blood cells clog the small vessels.\(^5\)\(^,\)\(^18\)\(^,\)\(^19\)

**Epilepsy**

DMPA may be associated with a reduction in the frequency of seizures in women with epilepsy.\(^25\)

**Diabetes mellitus**

A reduction in glucose tolerance has been observed in some women using progestogens.\(^3\)\(^,\)\(^4\) NET-EN has less effect on glucose tolerance, and is preferred to DMPA in patients with diabetes mellitus.\(^6\)

**Breast cancer**

Studies have provided evidence that there is no overall risk of breast cancer with DMPA. Women aged 35 years and younger at the time of cancer diagnosis, with the current or recent use of DMPA, showed a slight increased risk of breast cancer. All women diagnosed with breast cancer should discontinue hormonal contraception.\(^2\)\(^,\)\(^21\)

**Hypertension**

POICs may be used under medical supervision (WHO Category 2) by women with controlled hypertension, previous thromboembolism and cardiac disease.\(^1\)\(^,\)\(^2\)

**The vaginal transmission of human immunodeficiency virus or sexually transmitted infection**

Changes, such as thinning the vaginal mucosal epithelium, owing to the effect of progesterone, are thought to increase the risk of human immunodeficiency virus (HIV) transmission. Available epidemiological data have suggested a possible association between DMPA use and the risk of becoming HIV infected. However, there is no conclusive evidence that DMPA use increases the risk of sexually transmitted infections or HIV acquisition. Nevertheless, multi-purpose prevention measures are required to reduce HIV risk and unwanted pregnancies.\(^2\)\(^,\)\(^3\)\(^,\)\(^7\)\(^,\)\(^22\)\(^-\)\(^24\)

**Health education**

Education and counselling are effective ways of reducing discontinuation of the method owing to side-effects, such as menstrual changes and weight gain.

Regular clinic visits promote annual HIV testing, breast examination, Papanicoloau smear screening, blood pressure measurements and the promotion of condom use.

**Cost**

In view of the significant cost differentials and additional service delivery load associated with eight-weekly injections, the Department of Health recommends the use of DMPA. The following guidelines are recommended:

- New clients who initiate the use of injectable contraceptives should be given DMPA
- Women currently using NET-EN who have not previously used DMPA, should be given DMPA after receiving an appropriate, unbiased explanation for the change
- Women who then experience or who have in the past experienced unacceptable side-effects when using DMPA should be able to use or continue to use NET-EN.
Which injectable contraceptive should be chosen?

Depot medroxyprogesterone acetate

There are more data available on DMPA, and its effects are better known. It is marginally more effective than NET-EN, only needs to be given four times a year, and is cheaper for state and private patients.

Norethisterone enantate

NET-EN is suited to women who prefer the reduced likelihood of complete amenorrhoea, if a shorter return time to fertility is required, if the side-effects or disadvantages of DMPA are unacceptable or advisable, and if compliance with the eight-week return requirement is feasible.

Conclusion

POICS are widely used, and allow women to make choices on whether or not, or when, to have children. These effective contraceptives save healthcare costs, and pregnancy-related illnesses and mortality. It is important that providers remove unnecessary barriers to patients accessing POICS. A same-day start and extended return date can help women to manage successful contraceptive use. Initial and ongoing counselling is important and cost-effective in helping women to understand and manage any side-effects.

References