

1.1. Parenteral medroxyprogesterone and injection site necrosis and -atrophy

Introduction

Medroxyprogesterone is a progestogen which is used as systemic hormonal contraception. Parenteral medroxyprogesterone (Depo-provera[®], Megestron[®] and Sayana[®]) is a liquid suspension with a long term effect after intramuscular (Depo-Provera[®], Megestron[®]) or subcutaneous (Sayana[®]) injection. As solvent, water for injection with sodium chloride/hydroxide and polysorbate 80 are used. In the Netherlands Depo-provera[®] was registered in 1973, Megestron[®] in 1984 and Sayana[®] in 2007. Medroxyprogesterone is registered for *hormonal contraception when other forms of hormonal contraception are not suitable* [1-3].

The mechanism of action of medroxyprogesterone is based on the inhibition of gonadotropins from the pituitary gland which prevents follicular maturation. In fertile women a sustained inhibition of ovulation is given by medroxyprogesterone [1-3].

Injection site reactions occur after use of intramuscular or subcutaneous medroxyprogesterone. Local and systemic site reactions include erythema, urticaria, pruritus and discoloration [1-3].

Reports

On November 16, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports concerning injection site necrosis and four reports concerning injections site atrophy following administration of intramuscular or subcutaneous medroxyprogesterone, see Table 1 and 2. In reports A-D Depo-provera[®] was used, in report E and F Sayana[®] was the suspect drug.

Table 1. Reports of injection site necrosis with the use of intramuscular or subcutaneous medroxyprogesterone

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A 37838/37894* F, 31 – 40 years Pharmaceutical Company	medroxy-progesterone injection 150mg/ml contraception		injection site necrosis (12x4cm in her right buttock) liver function test abnormal	4 weeks after last injection unknown recovered after necrotomy
B 48856/48051* F, 31 – 40 years Pharmaceutical Company/ Physician	medroxy-progesterone injection 150mg/ml contraception		injection site necrosis (upper arm)	hours discontinued not recovered

*NB these reports are double reports.

Table 2. Reports of injection site atrophy with the use of intramuscular medroxyprogesterone

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
C 25385 F, 21 – 30 years Physician	medroxy-progesterone injection 150mg/ml contraception	amoxicillin/ clavulanate, salbutamol, fluticasone, prednisone,	Injection site atrophy (dimple in buttock)	Not reported Not reported Not reported
D 80422 F, 21 – 30 years Pharmacist	medroxy-progesterone injection 150mg/ml contraception		Injection site atrophy (dimple in upper leg) Fibromyalgia	12 months Not reported Not recovered (7 months after start reaction)
E 120778 F, 41-50 years Consumer	medroxy-progesterone injection 160mg/ml contraception		Injection site atrophy (2 dimples in her thigh)	Not reported Withdrawn Not recovered (7 months after the first and 4 months after the second reaction)
F 128022 F, 11-20 years Physician	medroxy-progesterone injection 160mg/ml contraception		Injection site atrophy	6 months Withdrawn Not recovered (1 year after start reaction)

Patient A concerns a woman aged 31-40 years with injection site necrosis (12x4cm in her right buttock) following administration of intramuscular medroxyprogesterone with a latency of 4 weeks after the last injection. The patient was admitted to a hospital and necrotomy was performed after which the patient recovered.

Patient B concerns a woman aged 31-40 years with injection site necrosis in her upper arm following administration of intramuscular medroxyprogesterone with a latency of hours after injection. The reporting physician states that an intravenous or intra-arterial injection could not be excluded because the patient's menstruation started directly after this injection. The patient will receive a skin transplantation because of the necrosis.

Patient C concerns a woman aged 21-30 years with injection site atrophy (dimple in buttock) after administration of intramuscular medroxyprogesterone.

Patient D concerns a woman aged 21-30 years with injection site atrophy (dimple in upper leg 7 cm in size and 0,5 cm in depth) 12 months after administration of intramuscular medroxyprogesterone. The patient used intramuscular medroxyprogesterone every 3 months from February 2007. In February 2008 she notices a dimple. The patient sometimes feels a mild stress on the area when she is walking and sometimes the dimple is sensitive without any movements. Recently she was seen by a rheumatologist and a diagnosis of fibromyalgia was made. The patient did not receive any treatment yet. An echography showed that the dimple is a scar on the muscle. No action was taken with medroxyprogesterone and at the time of reporting, 7 months after start of the reaction, the patient was not recovered.

Patient E concerns a woman aged 41-50 years with injection site atrophy (two dimples in her thigh) after administration of subcutaneous medroxyprogesterone, 7 months after the first injection was administered and three months after the second. Both injections caused a dimple which were not recovered at the time of reporting (respectively 7 and 4 months after injection).

Patient F concerns a woman aged 11-20 years with injection site atrophy 6 months after administration of subcutaneous medroxyprogesterone. According to the administering assistant the subcutaneous medroxyprogesterone was difficult to inject. The patient had not recovered one year after start of the atrophy.

Other sources of information

SmPC

The Dutch SmPC of intramuscular or subcutaneous medroxyprogesterone does not mention injection site necrosis or injection site atrophy [1-3].

Literature

Micromedex® [4,5] reports that in 5 clinical studies (n=2325) of subcutaneous medroxyprogesterone acetate suspension, 5% of women reported injection site reactions and 1% had persistent skin changes (ie, small areas of induration or atrophy).

Clarck and Lanigan [6] described a case report of injection site necrosis. It concerns a 33 year old woman who experienced extensive skin necrosis following a second intramuscular injection of medroxyprogesterone. The first injection into the right deltoid muscle was tolerated without complication. The second injection was administered, again into the right deltoid muscle. Within 30 min of the second injection she developed a burning sensation and erythema at the injection site, followed by a local urticated erythematous rash. Over the next few days the area surrounding the injection site, extending to an area of over 20 cm on the outer shoulder and upper arm, became progressively more painful with increasing dusky purple discoloration, and subsequent skin necrosis. Swabs taken from the area involved showed no growth. To cover the possibility of infection the woman was treated with oral ciprofloxacin, and the area dressed topically with silver sulphadiazine and subsequently with desloughing agents. After 3 months of topical therapy the area has healed to leave extensive scarring.

Clarck and Lanigan [6] reported that there was no published data about acute necrosis occurring at the injections site, however, one case of local skin necrosis and three cases of fat necrosis have been reported to the Committee of Safety and Medicines in the UK (personal communication).

Databases

Due to the limited number of reports of injection site necrosis associated with the use of intramuscular or subcutaneous medroxyprogesterone, the reporting odd ratio (ROR) was not calculated for the database of the Netherlands Pharmacovigilance Centre Lareb.

Table 3. Reports of injection site necrosis and -atrophy associated with medroxyprogesterone in the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO.

Drug	Number of reports	ROR (95% CI)
Medroxyprogesterone and injection site necrosis	WHO: 32	2.2 (1.6-3.2)
Medroxyprogesterone and	Lareb: 4	662.7 (199.5-2201.4)

Drug	Number of reports	ROR (95% CI)
injection site atrophy	WHO: 58	8.8 (6.8-11.5)

On November 24, 2011, the Eudravigilance database contained sixteen reports of injection site necrosis in association with medroxyprogesterone, which was reported disproportionately (ROR = 4.9, 95% CI: 3.0 – 8.0). All patients were females and the median age was 37 years (range 16 – 52 years). All reports were classified as serious. In four cases the criterion for seriousness was “disabling”, and in the remaining cases it was “other”

On the same date, the Eudravigilance database contained 31 reports of injection site atrophy in association with medroxyprogesterone, which was reported disproportionately (ROR = 52.9, 95% CI: 36.1 – 77.4). All patients were females and the median age was 27 years (range 14 – 45 years). Thirty out of thirty-one reports were classified as serious. In two cases the criterion for seriousness was “disabling”, and in the majority of the remaining cases it was “other”.

Prescription data

The number of patients using hormonal contraception for systemic use and the proportion of patients using medroxyprogesterone (Depo-provera[®]) in the Netherlands between 2008 and 2010 is shown in table 4.

Table 4. Number of patients using hormonal contraception or systemic and proportion of patients using medroxyprogesterone (Depo-Provera[®]) in the Netherlands.

	2008	2009	2010
G03A Hormonal contraception for systemic use	1,617,000	1,608,000	1,617,000
G03AC06 Medroxyprogesterone (Depo-provera[®])	60,084	60,336	63,920

Mechanism

The mechanism by which intramuscular or subcutaneous medroxyprogesterone induces injection site necrosis or injection site atrophy remains unknown. There are several drugs with the potential to induce skin necrosis, for example: anticoagulants (warfarin, heparin) and vasoconstrictors (β -blockers, noradrenaline). *Clack & Lanigan* [6] described that the clinical picture of their patient was similar to that seen with anticoagulant-induced skin necrosis, and although an underlying thrombophilic tendency was not detected, it may be that the process is in some way linked to platelet aggregation and thrombosis.

No biopsy were taken in the cases reported to the Netherlands Pharmacovigilance Centre Lareb or in the literature case motioned above. This makes it difficult to postulate a mechanism for necrosis induced by intramuscular or subcutaneous medroxyprogesterone.

Class-effects

Medroxyprogesterone belongs to the class ‘progestagens’ (other contraceptives). Although there are other progestagens available on the Dutch market, medroxyprogesterone is the only contraceptive on the market available as an injection. Levonorgestrel (Implanon NTX[®]) is available as a subcutaneous

implanted contraceptive. Seeing the nature of the reaction, a class effect is not possible for this reaction.

Discussion

Lareb received two reports of injection site necrosis and four reports of injection site atrophy with the use of intramuscular or subcutaneous medroxyprogesterone. The reports of injection site necrosis were severe. One patient was treated with necrotomy and the other patient would receive a skin transplantation.

The time to onset of the injection site necrosis was one hour to four weeks. One case report was found in literature. In this report skin necrosis started within a few days after administration [6]. Time to onset of the injection site atrophy was only reported in two reports; 6-12 months. It is also notable that the injection site necrosis or injection site atrophy did not always appear after the first injection of intramuscular or subcutaneous medroxyprogesterone.

To the best of our knowledge, no mechanism by which intramuscular or subcutaneous medroxyprogesterone induces injection site necrosis or injection site atrophy is found in the literature. In the literature one case report can be found. It is not excluded that the injection site necrosis was caused by an incorrect injection technique. The association between injection site necrosis and injection site atrophy with intramuscular or subcutaneous medroxyprogesterone is statistically supported by the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO.

Conclusion

These cases suggest a signal of injection site necrosis and injection site atrophy with the use of intramuscular or subcutaneous medroxyprogesterone. Consider to mention injection site necrosis and injection site atrophy in de SmPC of parenteral medroxyprogesterone.

- Consider to mention injection site necrosis and injection site atrophy in de SmPC of parenteral medroxyprogesterone

References

1. Dutch SPC Megestron®. (version date: 23-9-2010, access date: 3-11-2011) <http://db.cbg-meb.nl/IB-teksten/h09688.pdf>.
2. Dutch SPC Depo-Provera®. (version date: 5-7-2011, access date: 3-11-2011) <http://db.cbg-meb.nl/IB-teksten/h06602.pdf>.
3. Dutch SPC Sayana®. (version date: 11-10-2011, access date: 3-11-2011) <http://db.cbg-meb.nl/IB-teksten/h35305.pdf>.
4. Thomson Micromedex. Micromedex® Healthcare Series. (version date: 2011, access date: 22-11-2011) <http://www.thomsonhc.com/home/dispatch>.
5. Product information DEPO-SUBQ PROVERA 104 (TM) injectable suspension, medroxyprogesterone acetate injectable suspension 104 mg/0.65 mL. Pharmacia and Upjohn Co 2005 <http://www.thomsonhc.com/home/dispatch>
6. Clark SM, Lanigan SW. Acute necrotic skin reaction to intramuscular Depo-Provera. British Journal of Dermatology, 2000 2011;143(6):1356-7.

18-04-2012 In the period between the raising of this signal and placement on the website, the SmPC of Sayana® was updated and injection site atrophy is now included as an ADR.

This signal has been raised on February 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).