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Failed Lactation Associated with Medroxyprogesterone Acetate: Cases Series Assessment

Mulugeta Russom[1]*, Selamawit Gebrehiwet[1], Aziza Afendi[2], Elsa Mekonnen[1], Kifleyesus Tedla[3] and Dawit Tesfai[4]

[1]Pharmacists, Eritrean Pharmacovigilance Centre, Asmara, Eritrea
[2]Pharmacist, Eritrean Air Force Military Hospital, Asmara, Eritrea
[3]Gynecologist, Orotta National Referral Maternity Teaching Hospital, Asmara, Eritrea
[4]Pharmacist, Asmara College of Health Sciences, Asmara, Eritrea

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***Corresponding author:** Mulugeta Russom, Head, Eritrean Pharmacovigilance Centre, P.O. Box:212, Tel: +291-7197450; fax: +291-1-122899; E-mail: satiswt@gmail.com*

Abstract

Introduction: Depot-Medroxyprogesterone Acetate (DMPA) is not known to cause failed or suppressed lactation. The Eritrean Pharmacovigilance Center, however, received cases of failed lactation associated with the use of DMPA and the aim of this study is to assess this causal association.

Methods: Search on VigiFlow (national adverse drug reaction database) was made on June 15, 2016 with 'Medroxyprogesterone' as drug substance and 'failed lactation'/'puerperal lactation decreased' as a reaction term for the search criteria. The results generated exported to Excel for analysis. Naranjo Probability Scale and Austin Bradford-Hill criteria were used to assess the causality. Searches on VigiLyze were also made under the same search criteria to further assess the causal association.

Results: In the Eritrean Adverse Drug Reaction (ADR) database, VigiFlow, seven reports of failed lactation and decreased lactation associated with DMPA were retrieved. In all cases, the only suspected drug was DMPA and there was no other concomitant drug reported. Reaction abated following the withdrawal of DMPA in one of the cases. A total of 57 cases of suppressed or failed lactation associated with DMPA were retrieved from the WHO Global ADR database, VigiBase™ and the combination has an IC value of 4.28 with an IC025 value of 3.87. In all of the cases, no co-suspected drug was reported and in all but three, no concomitant drugs were reported.

Conclusion: This case series assessment suggests a causal association between DMPA and failed lactation which warrants further assessment on a larger population to substantiate the identified signal through highest epidemiological standard.

Abbreviations

DMPA: Depot Medroxyprogesterone Acetate; ADR: Adverse Drug Reaction; ICSRs: Individual Case Safety Reports; IC: Information Component; MedDRA: Medical Dictionary for Regulatory Authorities; WHO-ART: WHO Adverse Reaction Terminology

Introduction

Depot Medroxyprogesterone Acetate (DMPA) or Depo-Provera is an intramuscular injectable, progestin-only hormonal contraceptive that provides highly effective, long-acting and reversible contraception given in doses of 150mg/ml once every three months to prevent ovulation [1]. Its lack of estrogen makes it an excellent choice of hormonal contraceptive during all stages of lactation [2].

Previous evidence indicates that DMPA does not adversely affect the composition of breast milk or the milk supply [3-7]. The US-FDA prescribing information also states that milk composition, quality, and amount of milk are not adversely affected in nursing mothers treated with DMPA [8]. The association of DMPA with suppression of lactation is not also documented in the Summary of product Characteristics (SPCs) of the product [9]. The SPC of DMPA clearly states "the effect of DMPA in breast milk is not known".

A prospective cohort study which was non-randomized and non-blinded compared women who received either non-hormonal contraception (n = 52) or DMPA (n = 43) concluded that it has no detrimental effect on the duration and frequency of lactation within the first 16 weeks post partum [10]. Another prospective, non-randomized trial compared women taking DMPA (n = 102), another progestin-only contraceptive (n = 181) all administered before hospital discharge and non-hormonal contraception (n = 138). The authors concluded that progestin-only contraception initiated in the early postpartum period had no adverse effects on breastfeeding rates [11].

Despite all the above facts, the Eritrean Pharmacovigilance Center received cases of failed lactation and decreased lactation associated with the use of DMPA. The aim of this study is therefore, to assess the causal association of DMPA in the suppression or failure of lactation.

Methods

Search on VigiFlow (national adverse drug reaction database) was made on June 15, 2016 with 'Medroxyprogesterone" as drug substance and 'failed lactation'/'puerperal lactation decreased' as a reaction term for the search criteria. The results generated then exported to Excel spreadsheet for quantitative and qualitative signal analysis. All relevant data mining like disproportionality ratio or IC value, completeness score, rechallenge and dechallenge information of the Individual Case Safety Reports (ICSRs) were performed using VigiLyze™, a tool developed by the Uppsala Monitoring Center for data mining and analysis of ICSRs in VigiBase. Information Component (IC) value is the disproportionality measure of ICSRs in VigiBase. Positive IC value suggests a statistical signal. Onset dates, patient age/sex, and dates of administration of a medicine were checked to avoid any duplication of data.

To investigate alternative causes, possible risk factors for lactation failure were sought and assessed. Causality assessment was made individually using the Naranjo Probability Scale [12] and then subjected to case series assessment with the Austin Bradford-Hill criteria [13]. Literature and labeling of the adverse drug reactions were done by referring to the summary of product characteristics (SPC) of the product and reliable updated textbooks and published articles. Search on VigiLyze was also made under the same search criteria to further assess the causal association between Medroxyprogesterone and failed lactation. VigiLyze is an analysis tool of VigiBase, the WHO Global adverse drug reaction database, developed by the Uppsala Monitoring Centre.

Results

In the Eritrean national pharmacovigilance, VigiFlow, seven reports of failed lactation and decreased lactation associated with Medroxyprogesterone (reported between 2012 and July 2016) were retrieved (Table 1). Cases number two and three (Table 1) seem to be duplicated as they have same date of reaction onset, initiation of treatment, age of infant at reaction onset and are reported from same institution with different reporters. Not to overstate the problem, we decided to eliminate case number three and reduced the number to six. The age range of mothers and infants at time of reaction was 21-34 years and 1-6 months respectively except case number five (16 months). In all cases, the only suspected drug was DMPA and there was no other concomitant drug reported. In one of the cases, reaction abated following the withdrawal of DMPA (case number six). The causality assessment using Naranjo adverse drug reaction probability scale was found to be three probable and three possible (table 1). Results of the causality assessment obtained using Bradford-Hill criteria (table 2) showed significant association between DMPA and failed lactation.

Case Reports

Case 1

A 34 years old mother, who gave birth via spontaneous vaginal delivery to a healthy female neonate of 3.2Kg on 25th June of 2014, took Medroxyprogesterone injection (150mg/ml) with her preference on the same date. She is Para five mother who had never used any mode of hormonal contraceptive before. After four weeks she claimed that her breast is no more producing breast milk in which complete cessation occurred. As a consequence of the above reaction, the infant developed early malnutrition and was admitted to the pediatric ward on 28th of July received treatment accordingly. She had a heavy vaginal bleeding which started on the 11th July of 2014 and Norethistrone 5mg was given orally in which the symptom was alleviated. She denies any history of medical, surgical, psychiatric and gynecologic illness.

Table 1: Characteristics of the ADRs in VigiFlow indicating suppression/failure of lactation following the use of Medroxyprogesterone Acetate.

Case No.	Age (years)	Body Wt. (Kg)	Age of a baby at reaction onset	Reaction term	Interval from administration to reaction onset	Co-suspected (S), Concomitant (C) drug reported	Dose (mg/ml)	Seriousness	Causality	Reaction outcome
1.	34	52	1 month	Failed lactation	19 days	None	150	Yes	Probable	Not recovered
2.	21	_	45 days	Failed lactation	22 days	None	150	Yes	Possible	Not recovered
3.	27	_	45 days	Failed lactation	22 days	None	150	Yes	Possible	Not recovered
4.	32	62	4 months	Failed lactation	30days	None	150	Yes	Probable	Not recovered
5.	30	44	16 months	Failed lactation	Immediate	None	150	No	Possible	Not recovered
6.	24	70	6 months	Decreased lactation	33days	None	150	Yes	Possible	Recovered following drug withdrawal
7.	24	50	15 weeks	Decreased lactation	21 days	None	150	No	Probable	Unknown

Note: Case number 3 seem to be duplicated as all details except age are found to be same with case number 2.

Table 2: Causality assessment using Austin Bradford-Hill Criteria.

	Criterion	Outcome
1	Strength of association	IC=4.28, IC_{025}=3.87; shows statistical signal.
2	Consistency of data	Cases are reported from countries with wide geographical distribution. Clinically, the characteristics of the reported reactions from different parts of the world are consistent and the reaction time to onset was on around third week following administration of DMPA in majority of the cases (19 to 33 days).
3	Specificity of the association	The background incidence of lactation failure is quite low. In all the cases, only failed/suppressed lactation was reported following administration of DMPA. Besides, there were no co-suspected or concomitant drugs reported other than DMPA in all the cases from Eritrea and those retrieved from VigiBase except three cases with concomitants.
4	Temporal relationship	Reaction commenced following administration of the DMPA with plausible time to onset.
5	Dose-response relationship	DMPA is taken every three months or on stat basis. Hence, it is difficult to establish dose-response relationship. One case with suppressed lactation however, recovered after about two months just before the next dose.
6	Biological mechanism or plausibility	Though not proven on ground, progesterone interferes with prolactin binding to the receptors on the alveolar cells within the breast, thereby directly suppressing milk production [14,15].
7	Experimental evidence	One case reported with positive dechallenge.
8	Analogy	Not applicable
9	Coherence	Not applicable

IC information component

She also denies any history of drug intake, smoking or alcohol use. She is married, works in a hospital as an Associate Nurse and had modest monthly income. She used to breastfed appropriately to her elder children in which she denies use of pacifier.

Case 2

A 32 years old Para-III mother had history of Medroxyprogesterone since she gave birth to her second child and faced cessation of lactation after she took Medroxyprogesterone. The first incidence was on 2013 when she had her first birth and she took it after one and half month (6 weeks) of post partum period in which at third month complete cessation of milk occurred. As consequence, it led to early weaning with cow's milk and other additives. The second incidence occurs in 2015 (that is on her second birth), she took it on third month of post partum period and it started to decrease after one month of administration and lactation finally failed two months after the administration of Medroxyprogesterone 150mg/ml. In both incidences, she had no history of other drugs, herbal intake, chronic diseases and other medical related conditions.

Case 3

A 24 years old primi-para mother took first dose of Medroxyprogesterone three months after giving birth to a term with normal body weight presented with decreased milk expression such as extreme irritability of the infant, no progressive change in body weight and development which has started 3 weeks following Medroxyprogesterone injection and got worsened at 5th month after giving birth. As a consequence, the infant got admitted due to severe protein energy malnutrition and diluted F-100 was given as therapeutic feeding. The mother was advised to start her child on formula milk and to avoid using Medroxyprogesterone injection during the first 6 months of post partum period. The mother had no history of diabetes, hypertension and anemia. Infant was fully investigated and no apparent organic illness was revealed.

Reports in the WHO Global Database, VigiBase™

In the WHO Global ICSRs database, VigiBase™, a total of 57 cases were retrieved (reported between 1994 and August 2016) which are reported from USA(49), Eritrea (4), United Kingdom(2) and Canada (2). The reported reaction terms lactation puerperal decreased (48), failed lactation (6) and lactation disorder (3) are all labeled with MedDRA term of suppressed lactation and WHO-ART term of lactation puerperal decreased. The association of suppressed lactation and DMPA has an IC value of 4.28 with an IC_{025} value of 3.87. In all of the cases, no co-suspected drug was reported and in all but three, no concomitant drugs were reported.

Discussion

Causality assessment of the ADRs retrieved from the Eritrean Pharmacovigilance database suggests that there is a causal association between DMPA and failed lactation. The association is fore grounded through a disproportionality analysis with an IC value of 4.28 and an IC_{025} value of 3.87. IC value is a statistical disproportionality measure based on the observed and expected numbers of ICSRs submitted to the WHO global database. A positive IC value indicates that cases are highly reported than expected and suggests a statistical signal.

Despite the fact that failure or suppression of lactation can be affected by a number of social and environmental factors, other possible alternative causes like history of other drugs intake, depression, smoking, diabetes, mixed feeding, obesity and other

relevant medical conditions were ruled out in four of the cases (cases number 1, 4, 6 and 7 on table 1). However, this does not guarantee for absolute exclusion of other explanations that could on their own possibly cause the reaction.

In one case (case number 6), reaction abated slowly following discontinuation of the suspected drug, DMPA. In case report number two, the mother had experienced failure of lactation twice following administration of DMPA. Besides, there were no co-suspected or concomitant drugs reported other than DMPA in all the cases from Eritrea and those retrieved from VigiBase except three cases with concomitants. The cases in VigiBase are reported from Americas, Europe and Africa; which shows wide geographical distribution.

The physiology of lactation initiation and maintenance requires the elevation of prolactin hormone, which indirectly indicates the fall of progesterone in blood. The possible mechanism of action is that progesterone interferes with prolactin binding to the receptors on the alveolar cells within the breast, thereby directly suppressing milk production [14,15]. However, it is good to note that there is no concrete clinical study that proved this on ground.

The plausible temporal relationship with consistent time to reaction onset in most of the cases, the high disproportionality ratio (IC Value), the unavailability of other reported alternative explanations of the adverse effect, the positive dechallenge in one case, the plausible biological mechanism and the wide geographical distribution of the cases are therefore evidences that support a causal association between DMPA and failed lactation.

Early cessation of breastfeeding due to the suspected drug, DMPA, in our case caused severe protein energy malnutrition in three of the infants which led to hospital admissions. Failure of lactation before six months post partum can also lead to mortality and decreased cognitive development in infants [16]. Hence, the association requires further assessment to provide sound decision making on its safe use during post-partum period.

A number of studies conducted to investigate the effect of DMPA on lactation do not found causal association. On the other hand, studies done by Brownell, et al. [17] and Truitt, et al. [18] on their systematic review concluded that previous empirical researches including randomized controlled trials are inconclusive regarding the effect of DMPA on lactation due to methodological flaws either in study design or analysis. Hence, given the presence of a convincing biologic mechanism describing the potential deleterious effect of DMPA use on lactation and the overall absence of methodologically rigorous studies, they recommend results to be interpreted with caution and urged the need of further properly conducted randomized controlled trial of adequate size with the highest epidemiologic standards to address this issue.

From this case series assessment, it can be concluded that there is a suggestive causal association between DMPA and failed or suppressed lactation. Early cessation of breastfeeding secondary to the DMPA caused severe protein energy malnutrition on some of the infants which led to hospital admissions. Hence, failure of lactation associated with DMPA warrants immediate assessment on a larger population to substantiate the important safety signal through highest epidemiological standards.

Authors' contributions

MR, SG, AA, KT, EM and DT played a key role in data analysis and interpretation. MR, SG and AA wrote the article and edited by the rest of the authors.

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