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Etonogestrel implant migration to the vasculature, chest wall, and distant body sites: cases from a pharmacovigilance database☆,☆☆

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Abstract

Objective: To describe clinical outcomes of etonogestrel implant patients with migration to the vasculature, chest wall and other distant body sites spontaneously reported to the US Food and Drug Administration Adverse Event Reporting System (FAERS) database.
Study design: We performed a standardized Medical Dictionary for Regulatory Activities (MedDRA) query in the FAERS database (through November 15, 2015), with reports coded with one or more MedDRA preferred terms that indicate complications with device placement or migration of the device from the original site of insertion to the vasculature, chest wall and other distant body sites. We excluded any cases previously described in the medical literature.
Results: We identified 38 cases of pronounced etonogestrel implant migration. Migration locations included the lung/pulmonary artery (n=9), chest wall (n=1), vasculature at locations other than the lung/pulmonary artery (n=14) and extravascular migrations (n=14) to other body sites (e.g., the axilla and clavicle/neck line/shoulder). The majority of cases were asymptomatic and detected when the patient desired implant removal; however, seven cases reported symptoms such as pain, discomfort and dyspnea in association with implant migration. Three cases also describe pulmonary fibrosis and skin reactions as a result of implant migration to the vasculature, chest wall and other distant body sites. Sixteen cases reported surgical removal in an operating room setting.
Conclusions: Our FAERS case series demonstrates etonogestrel implant migration to the vasculature, chest wall and other body sites distant from the site of original insertion.
Implications statement: As noted by the sponsor in current prescribing information, a key determinant in the risk for etonogestrel contraceptive implant migration appears to be improper insertion technique. Although migration of etonogestrel implants to the vasculature is rare, awareness of migration and education on proper insertion technique may reduce the risk.
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Keywords: Contraceptive implant; Migration; Intravascular; Pulmonary artery; Lung; Chest wall

1. Introduction

Contraceptive implants are an important and effective option for family planning. Worldwide prevalence of contraceptive use has significantly increased over the last four decades, with substantial variability in the proportion of women who use implants in different parts of the world [1]. In 2015, approximately 1% of the total worldwide contraceptive use was met with contraceptive implants, with the United States having a similar usage pattern [1].

In the United States, one approved contraceptive implant is currently available. The etonogestrel 68-mg implant is inserted in the inner side of the upper arm to provide highly effective reversible contraception. Implanon® (Merck & Co., Inc., formerly Organon USA, Inc., Kenilworth, NJ, USA) was first approved by the US Food and Drug Administration (FDA) in 2006. Nexplanon® (Merck & Co., Inc., Kenilworth, NJ, USA), FDA approved in 2012, added barium sulfate to the implant and used a new inserter that allows for a one-handed technique for insertion, in contrast to Implanon's two-handed approach [2]. The new product is marketed as Implanon NXT® (Merck Sharp & Dohme) in several countries outside the United States. The sponsor stopped Implanon distribution in the United States as of

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December 2012 [3], although existing stock of Implanon already distributed in the US market could still be inserted. In addition, Implanon is still being marketed in countries outside the United States.

Since the approval of these implants, the FDA-approved prescribing information (i.e., product labeling) has conveyed that the implant should be inserted subdermally, avoiding the sulcus between the biceps and triceps muscles. Since February 2009, the prescribing information also notes reports of local implant migration and provides advice on confirmation of a nonpalpable implant, including at the time of insertion or removal [4]. These steps may involve the use of imaging techniques such as ultrasound or magnetic resonance imaging for Implanon, or either of these techniques as well as two-dimensional X-ray, and computerized tomography scan for Nexplanon to locate a nonpalpable implant [4,5].

In September 2015, the sponsor of Nexplanon updated the prescribing information to warn of potential implant insertion and removal complications and to describe migration to vessels of the arm and to the pulmonary artery. The prescribing information also states that, "incorrect insertion including deep insertion may be related to the implant migration" [6]. Implant expulsion or migration, including to the chest wall, is also noted under the Postmarketing Experience section of the prescribing information [6]. Updated prescribing information provides more specific instructions regarding insertion. The prescribing information also provides advice on localizing and removing a nonpalpable implant, including the possible need for imaging techniques to the chest and surgical removal involving providers familiar with the anatomy of the chest [6].

In October 2015, the sponsor also issued a "Dear Health Care Provider" letter to alert clinicians in the United States about updates in prescribing information and patient product information (e.g., insertion, localization, removal and migration of the implant). The purpose of this report is to describe cases of pronounced etonogestrel implant migration that have been submitted to the FDA Adverse Event Reporting System (FAERS) database.

2. Materials and methods

We identified cases from the FAERS database. The FAERS database contains reports (also known as MedWatch reports) of adverse drug events and medication error reports submitted to the FDA. These reports are submitted directly from the public or sponsors. In order to retrieve US and non-US postmarketing adverse event reports of etonogestrel implant migration, we performed a standardized Medical Dictionary for Regulatory Activities (MedDRA) query in FAERS for reports with regulatory serious outcomes through November 15, 2015. The FDA defines a serious adverse drug experience as one that results in an outcome of death, life-threatening condition, hospitalization (initial or prolonged), disability, congenital anomaly or other serious important medical event. We queried FAERS reports coded with one or more MedDRA preferred terms for implant migration (i.e., *Complication of removal*, *Device adhesion issue*, *Device deployment issue*, *Device dislocation*, *Device embolisation*, *Embedded device*, *Medical device complication*, *Migration of implanted drug*, and *Vascular access complication*). We defined a case as any report describing pronounced etonogestrel implant migration to the chest wall; vasculature such as the lungs, pulmonary artery or other reported blood vessels; or other body sites distant from site of original insertion such as axilla, clavicle or shoulder. We compiled this case series to describe pronounced migrations as reported to FAERS.

Sponsors often report literature cases to FAERS. For this report, we excluded any cases previously documented in published medical literature.

3. Results

We identified 38 unique cases that met the criteria for inclusion in the case series [Nexplanon/Implanon NXT (n=20) and Implanon (n=18)]. The patients had a median age of 28 years (range, 15–47 years) and the cases originated from France (n=14), United States (n=9) and other countries (n=15) in Europe, Asia, South America, Africa and Oceania. The FDA has received an increasing number of reports for etonogestrel implants migration since 2013 (Fig. 1). We received 30 FAERS cases in 2014 and 2015 [Nexplanon/Implanon NXT (n=17) and Implanon (n=13)], 23 of which describe migrations occurring outside the United States.

The 38 cases noted migration to the following locations (Table 1): the lung/pulmonary artery (n=9), chest wall (n=1), vasculature at locations other than the lung/pulmonary artery (n=14) and other body sites including axilla (n=11) and clavicle/neck line/shoulder (n=3). While the majority of cases were detected when the patient desired implant removal, 7 of 38 cases reported symptoms that could be attributed to migration of the implant including pain, discomfort and dyspnea. Other clinical outcomes of these migrations included pulmonary fibrosis around the implant (n=2), skin reaction (n=1) and a patient with a desire for pregnancy with unsuccessful removal attempt (n=1). We identified no fatal cases. Twenty-one cases noted the following insertion locations: subdermal (n=11), sulcus between biceps and triceps (n=6), subcutaneous (n=2), intramuscular (n=1) and intravenous (n=1). The remaining 17 of 38 cases, including 2 cases noting deep insertion, lack details regarding the insertion location (Table 1).

Pronounced migration of implants required multiple methods for detection and removal (Table 1). Sixteen of the 38 cases reported surgical removal in an operating room setting, including lung segmentectomy (n=1) and thoracotomy (n=1). Three cases described the implant removal under local anesthesia. An additional seven cases described unsuccessful removal attempts that included surgical, local and one unspecified procedure. The most frequent reason