CASE REPORT

Intravascular migration of contraceptive implants: two more cases

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Conflicts of interest

All three authors have received fees for acting as trainers and for giving lectures on behalf of companies that market contraceptive implants. MW is contracted by MSD to perform complex implant removals in the UK.

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Abstract

Cases: In addition to previously published case reports, further cases of intravascular migration of contraceptive implants have been identified from an information request to two national adverse reaction spontaneous reporting systems. We report on two new cases of insertion into the venous system with subsequent embolism to a pulmonary artery. **Conclusion:** Incorporating barium sulfate into the implant has facilitated diagnosis of these very rare adverse events with the initial diagnosis of embolism to the pulmonary arterial tree made by chest X-ray. Removal of an implant from a segmental branch of a pulmonary artery is technically challenging and not without risks. Unsuccessful removal appears to be preceded by a delay in diagnosis leading to endothelialisation of the implant in the pulmonary arterial wall. **Implications:** Subdermal placement of contraceptive implants over the anterior surface of the biceps rather than in the sulcus between the biceps and triceps may negate this rare but reported risk.

Keywords: contraceptive implant, intravascular, lung, pulmonary embolism, pulmonary artery

1. Introduction

The single-rod etonogestrel implant Implanon was available in the UK between 1999 and 2010. We were aware over this eleven-year period that implants occasionally 'go missing' in the body and cannot be localised[1]. Positive etonogestrel (ENG) blood tests confirmed the presence of the implant but these non-radiopaque implants were difficult to demonstrate using imaging techniques. We could not confirm our suspicions that these implants were located in the lung [2]. However, we felt inadvertent insertion of an implant intravascularly and transit in the venous system to the pulmonary arterial system was possible. One of the authors (DM) has seen two patients in which the key features in the clinical history included painful implant insertion over the area of the sulcus between the biceps and triceps, the site previously recommended by the manufacturers. In both cases there was associated extensive bruising over the upper arm with the distal end of the implant being easy to feel initially and then becoming impalpable. High frequency ultrasound scanning and magnetic resonance imaging of the arm, chest X-rays and computerised tomography scans failed to locate the implants.

The advent of a modified radiopaque implant and applicator (proprietary name Nexplanon in some countries and Implanon NXT in others) in 2010[3] makes the imaging and evaluation of these 'lost implants' easier.

Individual case reports of suspected adverse reactions which are sent to regulators spontaneously by health professionals, pharmaceutical companies and users of medicines themselves are used to detect 'signals' and generate hypotheses of a possible link between a medicine and an adverse effect[4]. The UK's Yellow Card Scheme is an example of such a spontaneous reporting system (https://yellowcard.mhra.gov.uk/). Data derived from Yellow Cards are publicly available for each drug in the form of Drug Analysis Prints (www.mhra.gov.uk/drug-analysis-prints/). It is important to note that the inclusion of a reported reaction in a Drug Analysis Print does not necessarily mean it has been caused by the drug or its delivery vehicle, only that the reporter had a suspicion it may have. The fact that symptoms occur after use of a drug, and are reported via the Yellow Card Scheme, does not in itself mean that they are proven to have been caused by the drug/vehicle. The Drug Analysis Prints for etonogestrel implants show 23 reported cases of pulmonary embolism. An additional category of 'device embolisation' was added in 2014; the tally for device embolisation currently stands at 1 (period ended 4 April 2016).

2. Enquiry to the British and Irish drug regulators

Author involvement with the published cases (MW, SR) in both the UK and the Republic of Ireland (Cases 1 – 5, Table 1) led us to wonder whether there were any further cases in these two countries. We asked the UK Medicines & Healthcare products Regulatory Agency (MHRA) about spontaneous reports of such cases through the UK Yellow Card Scheme. We also asked the Irish Health Products Regulatory Authority (HPRA) about any cases reported to their national database of suspected adverse reactions.

3. Cases identified

Four cases of etonogestrel implant migration to other sites of the body were reported to the UK MHRA between 2010 and 2016, including Case 1 of the published cases. One of these four cases could not be confirmed to be in the lung by the reporter; the implant appeared to be in the chest wall. There is, thus, a total of two UK cases not previously in the public domain (Cases A and B, Table 1). The implants involved in both cases were Nexplanon. Information about the cases is anonymised

and limited due to the need for confidentiality to protect individuals' identities. For example we were not permitted access to the women's ages. Also some reports to the regulator contain sparser information.

A single case was known to the Irish HPRA and this was confirmed to have already been the subject of a published case report (Case 3, Table 1).

4. Discussion

There is one case in the literature in which an implant was reported to have been inserted into the peripheral arterial system[5]. This involved the brachial artery and was associated with profuse bleeding. Thrombus formed in the artery which became occluded. Normal arterial circulation was restored after vascular surgery.

All other published case reports are about inadvertent insertion of implants into the venous system. This is very rare with five cases published over the last two years (Cases 1 – 5, Table 1). These five case reports from three adjacent countries in Western Europe[6-10] have been written by radiologists, thoracic surgeons and emergency medicine specialists. All five reports relate to the radiopaque version of the etonogestrel implant. There is emphasis on the subtleties of various forms of imaging but little clinical detail. However, the cases are remarkably similar in their clinical presentation and findings. In all five, the implant was not palpable in the arm and the rod showed clearly on a chest X-ray.

A major limitation of this case report is the limited information that the MHRA was able to release to us about the two further cases that were reported to them; this was due to strict internal rules about information exchange designed to protect patient and reporter confidentiality.

Heudes *et al* explained[9] the intravascular journey of the implant as it travels through veins in the upper arm (from the basilic vein to the axillary vein which becomes the subclavian vein) into the superior vena cava, right atrium, through the tricuspid valve into the right ventricle and thence into the pulmonary trunk. The rod is then carried into either the left or right pulmonary artery and along their successive segmental branches until it finally lodges as an embolus in an arterial branch with a diameter similar to the 2mm wide rod. The left lower lobe is a favoured site in the lung.

In three out of five cases the women experienced chest pain. Case 3 was associated with a pneumothorax. Four of the cases had positive etonogestrel levels. Case 4 had haematoma formation

at the insertion site in the arm immediately after the insertion. Case 5 was on steroids for an auto-immune condition. No lung infarction or arterial thrombosis was reported.

When facing this complication, women react differently. Case 1 did not contemplate any intervention initially. Others immediately decided to undergo interventional radiological procedures where a wire and snare was introduced into the pulmonary artery via an accessible vessel in the groin or neck. This may be unsuccessful, as in the case described by O'Brien *et al*[8], where the rod had become endothelialised in the arterial wall and removal risked arterial rupture. In France thoracoscopy has been a successful mode of removal. Case 3 was offered such a procedure but declined. Women may feel that open thoracotomy, if offered, would be a step too far in terms of invasiveness.

We advise that when a radiopaque contraceptive implant cannot be located in either arm by usual imaging techniques, a chest X-ray should be considered. One of the authors (MW) facilitated the diagnosis in Case 1 by recommending a chest X-ray and both of the other UK cases were reported through the Yellow Card Scheme following location by chest X-ray. Clinicians need to 'think the unthinkable' in these cases.

When contraceptive implants are inserted intravascularly women face the real possibility of persistent side-effects, commonly irregular vaginal bleeding and the theoretical possibility of pulmonary arterial thrombosis and infection. Younger women may potentially be rendered involuntarily infertile. ENG blood levels above 90 pg/mL inhibit ovulation. A US study showed median blood levels of 177 pg/mL (range 68 – 471 pg/mL) at four years compared to 189 pg/mL (range 64 – 803 pg/mL) at three years[11]. We calculate that there would be continued release of ENG from the implant for at least six years if 30 mcg is the average release rate each day.[12]. However, nothing is known about the release characteristics when an implant is located intravascularly rather than its usual subdermal position. In such women artificial reproductive technology may enable ovulation and fertilisation but the endometrium is unlikely to respond favourably to exogenous hormone.

We know little about the length of time to diagnosis of intravascular implant embolism in these cases. There may have been a delay, with health care professionals concentrating on imaging the arm to find the implant and then seeking help from tertiary level specialists. Women may then need time to consider whether they undergo a major procedure. The implant in Case 3 had been present for two years and endothelialisation in the artery may have complicated its removal [8]. Case 1 presented seven months after insertion and Case 5 ten months after insertion; the latter was removed successfully.

We know nothing about predisposing factors in these cases. Intuitively this complication would seem more likely to occur when implants are fitted in the sulcus between the biceps and triceps and there is little subcutaneous tissue such as in very thin women.

We know nothing about the qualifications or training of the operators who inserted these implants. All we know is that the operator in Case 5 was a general practitioner. It should be noted that the Summary of Product Characteristics (SmPC) recommends that healthcare professionals in Europe have completed training for the use of the etonogestrel implant applicator prior to insertion and removal of the implant.

In light of the 2015 Montgomery case in the UK Supreme Court[13], patients need to be told about risks of a procedure even if the risk is very small. A material risk is defined as that which a reasonably prudent patient thinks is significant. UK law now demands a standard of consent broadly similar to that required by the professional guidance of the UK General Medical Council and more in line with many other jurisdictions.

When inserting a contraceptive implant the neurovascular bundle lying beneath the sulcus between the biceps and triceps should be avoided[14]. Subdermal placement of contraceptive implants over the anterior surface of the biceps may reduce the risk of intravascular insertion into the basilic vein or other veins in the vicinity. This was suggested by more than one authority ten years ago[15;16]. Tenting the skin is also imperative; the modified applicator (involved in all seven cases described here) is not sufficient in itself to set the depth of the implant[17]. Direct visualisation of the tip of the needle throughout the insertion procedure is necessary, as recommended for avoidance of deep insertion[17]. Unfortunately, the redesigned applicator restricts the view of the needle [18] therefore clinicians are advised to sit or tilt the applicator to ensure subdermal placement.

We recommend that all health care professionals carrying out contraceptive implant insertions and removals receive approved training. In the UK this is the Letter of Competence in Subdermal Contraceptive Implant Techniques (Faculty of Sexual & Reproductive Healthcare, www.fsrh.org).

The SmPC and Package Leaflet for Nexplanon/Implanon NXT have been revised in the UK and Ireland and 'Dear Health Care Professional' letters in relation to intravascular insertion were sent out in May 2016. We are pleased that the SmPC wording now mentions avoidance of the sulcus but are not so content that the SmPC diagram recommends placement over the triceps muscle. Migration to the pulmonary vasculature is now mentioned.

5. Conclusions

We suggest that intravascular migration of implants into the pulmonary vascular tree is not a new phenomenon. It has come to light because of the addition of barium sulfate to the single-rod implant product. We surmise that pre-2010 cases of implants in the lung have been missed as the rods were not radiopaque.

The category of 'device embolisation' added to the classification of adverse reaction spontaneous reports by UK regulators in 2014 is helpful.

Now that there are published case reports in addition to company data about inadvertent intravascular insertion of contraceptive implants, clinicians must mention this as a very rare complication in order for consent to be valid. Although a serious adverse event, intravascular insertion is estimated by MSD to occur in only 1.3 cases per million radiopaque implants sold.

A chest X-ray should be considered in all cases of impalpable implants not located by high frequency ultrasound where ENG assays are positive. Women found to have an implant in the pulmonary arterial tree need referral to a thoracic surgeon who will liaise with their interventional radiology colleagues over proposals for the best removal technique. We believe that early diagnosis is desirable not only to resolve the uncertainty of the implant's location but to help prevent endothelialisation of the implant in the pulmonary artery complicating the implant's removal. When an implant cannot be removed women face at least six years of progestogen release from the rod.

Implants should be sited at least 1 cm anterior to the sulcus between the biceps and the triceps. Subdermal placement needs emphasising, with clinicians making every effort to tent the skin at the time of implant insertion with the newer applicator, as they did with the previous version. Direct visualisation of the needle is needed throughout the insertion procedure.

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Table 1 Summary information about published cases and cases reported to the regulator of insertion of contraceptive implants into the venous system and intravascular migration to the pulmonary tree

Case	Country	Publication/ report to regulator	Age of woman at diagnosis	Location	Outcome
1	UK	Patel et al 2014[6]	36	Left lower lobe	Woman declined any intervention*
2	France	D'Journo et al 2015[7]	20	Left lower lobe	Segmentectomy via video-assisted thoracoscopy
3	Ireland	O'Brien et al 2015[8]	23	Left lower lobe	Failed removal attempt by interventional radiology
4	France	Heudes et al 2015[9]	18	Right upper lobe	Successful removal by interventional radiology
5	France	Maroteix et al 2015[10]	27	Left lower lobe	Successful removal by interventional radiology
A	UK	Spontaneous report 2013	NK	NK	Failed interventional radiological attempt at removal
B	UK	Spontaneous report 2016	NK	NK	NK

*As a result of author involvement with this case (MW), we know that this woman subsequently underwent an interventional radiological procedure 12 months after insertion which was unsuccessful.

NK = not known