Open Access Journal of Contraception

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

Failure of Implanon® on antituberculous therapy

This article was published in the following Dove Press journal:
Open Access Journal of Contraception
8 September 2010
Number of times this article has been viewed

Babatunde A Gbolade

Fertility Control Unit, Department of Obstetrics and Gynaecology, St James's University Hospital, Leeds, West Yorkshire, UK

Abstract: Implanon®, a contraceptive implant, is increasingly being used because of its efficacy and nonuser-dependent nature. However, as for other steroid contraceptives, its efficacy can be reduced by enzyme-inducing drugs, such as antituberculous medication, resulting in unplanned pregnancy. We present the case of a 27-year-old para 1 + 0 referred to us for termination of a pregnancy that resulted from failure of Implanon during concomitant treatment with Rifinah® (a rifampicin-isoniazid combination). All health care providers should be aware of the adverse effects of hepatic enzyme inducers on hormonal contraceptives, obtain details of current contraceptive methods from women of reproductive age, and refer them to contraceptive and reproductive health care professionals as appropriate for optimal management. This will ensure that such women do not experience the psychologic trauma of a termination of pregnancy.

Keywords: etonogestrel implant, Implanon, contraceptive failure, unintended pregnancy, enzyme inducer, rifampicin

Introduction

Implanon® (Organon Laboratories Ltd, Cambridge, UK), a single-rod contraceptive implant is one of the most efficacious of the currently available contraceptive methods,[1,2] and is the only one marketed in the UK, where it was launched in October 1999 after marketing authorization was obtained on June 9th, 1999.[3] Since then, there has been a steady increase in its use by women of reproductive age in England,[4,5] especially following the National Institute for Health and Clinical Excellence (NICE) publication of its guidance on long-acting reversible methods of contraception in 2005.[2] More than 4.5 million women have used Implanon worldwide.[6] It is 4-cm long, with a diameter of 2 mm, and is made of an ethylene vinyl acetate copolymer with a core containing 68 mg of etonogestrel (3-keto-desogestrel) for subdermal insertion in the inner aspect of the nondominant arm. Its main mechanism of action is ovulation suppression, augmented by increased cervical mucus viscosity that hinders the passage of spermatozoa and alters the endometrial lining,[7] and it is independent of user compliance. Following insertion of Implanon, etonogestrel is rapidly absorbed into the circulation, ovulation-inhibiting concentrations being reached after eight hours and maximum serum levels by the fourth day after insertion. Serum levels then decline slowly over the next three years. After removal, serum etonogestrel levels are undetectable within one week,[8] and ovulation returns in most women after 3–4 weeks.[9]

Although there were no failures resulting in pregnancies in the original studies of Implanon, several pregnancies with Implanon *in situ* were reported in post-marketing surveillance studies in Australia[10] and France.[11] However, most of these Implanon "fail-

Correspondence: Babatunde A Gbolade
Fertility Control Unit, Department of Obstetrics and Gynaecology, St James's University Hospital, Beckett Street, Leeds LS9 7TF, West Yorkshire, UK
Tel +44 113 206 7135
Fax +44 113 206 5381
Email b.a.gbolade@leeds.ac.uk

submit your manuscript | www.dovepress.com
Dovepress
DOI: 10.2147/OAJC.S12194

ures" were attributed to faulty insertion technique, insertion at the wrong time during the menstrual cycle, insertion while already pregnant, expulsion of the implant, or drug–drug interaction. No pregnancies occurred in other post-marketing surveillance[12,13] or clinical studies,[14] confirming the need for health care providers to undergo proper training and certification before providing the service.[15]

Case presentation

We present the case of a 27-year-old para 1 + 0 referred to us for consideration of termination of an unplanned and unwanted pregnancy. She had had Implanon inserted six months earlier in a community family planning clinic, but subsequently commenced use of the antituberculous medication Rifinah® (rifampicin-isoniazid) prescribed by a different hospital department. She maintained that when she was commenced on antituberculous therapy, she was not advised to use additional contraception or change to another method, even though she mentioned that she was using Implanon for contraception. She was uncertain about the date of her last menses, but transvaginal ultrasound examination revealed a single viable intrauterine pregnancy of seven weeks' duration. Following a full discussion about her options, she chose to terminate the pregnancy, have the Implanon removed, and replaced with a copper intrauterine device. These procedures were undertaken without any complications. She was due to complete her antituberculous therapy a few weeks later and, to the best of our knowledge, has remained well. Written informed consent was obtained from the patient for publication of this case report.

Discussion

Drug interactions with hormonal contraceptives are of concern, particularly when steroid metabolism is enhanced, because this may reduce contraceptive efficacy. The cytochrome P450 (CYP) enzyme system in the liver plays a significant role in drug metabolism, and drugs (possibly including the herbal medication, St John's Wort) that induce these enzymes can cause increased elimination of contraceptive steroids, resulting in reduced reliability and, consequently, unplanned pregnancy.[3] A variety of potent enzyme inducers known to have deleterious effects on hormonal contraceptives include some antiepileptics (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, topiramate),[16–19] antibiotics (rifampicin, rifabutin),[20–24] antifungals (griseofulvin),[25] protease inhibitors (amprenavir, atazanavir, nelfinavir, lopinavir, saquinavir, ritonavir),[26] and non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine).[27] There have been sporadic reports of Implanon failure due to suspected interaction with concomitantly administered drugs, resulting in intrauterine[10,11,28] or ectopic[29–31] pregnancies. Two of these pregnancies were directly associated with concomitant use of rifampicin.[10,29]

This woman was treated with rifampicin-isoniazid while using Implanon. Etonogestrel is metabolized by the CYP3A4 enzyme system and rifampicin is known to induce and isoniazid to inhibit certain CYP enzyme systems, particularly CYP3A4 and other Phase I and Phase II enzyme systems in the liver.[10] While the impact of the competing effects of rifampicin and isoniazid on the metabolism of drugs that undergo biotransformation through the affected pathways is unknown,[32] this enzyme induction is likely to reduce the plasma concentrations of etonogestrel. Although no definite interaction studies have been performed with etonogestrel, rifampicin is known to cause a 55% reduction in the area under the concentration-time curve in pharmacokinetic drug interaction studies.[33] When extrapolated to etonogestrel, it would explain the failures resulting in pregnancies. The summary of product characteristics for Implanon contains recommendations for women using Implanon, while being treated concomitantly with rifampicin or other potent microsomal enzyme inducers. It states that:

> "Women on treatment with any of these drugs should temporarily use a barrier method in addition to Implanon. With microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. In women on long-term treatment with hepatic enzyme-inducing drugs, it is recommended to remove Implanon and to prescribe a non-hormonal method. The prescribing information of concomitant medications should be consulted to identify potential interactions".[32]

We suggest that these recommendations should be followed assiduously.

Conclusion

This case report illustrates the potential for adverse events without cross-specialty interaction in the management of patients. Despite mentioning that she was using Implanon when she was commenced on antituberculous therapy, the significance of this was not recognized. Health care providers looking after women of reproductive age should obtain details of their current contraceptive methods and check the prescribing information of drugs to be used concomitantly, to identify potential interactions. If necessary, they should consult others with the necessary information and expertise to obtain optimal benefits for their patients.

Disclosure

The principal author has received financial support from Organon Laboratories Ltd (manufacturers of Implanon) to attend conferences and sponsorship of lunch for delegates attending our Diploma of the Faculty of Sexual and Reproduction Healthcare theory courses.

References

1. Affandi B. An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon. *Contraception*. 1998;58:99S–107S.
2. National Collaborating Centre for Women's and Children's Health (Commissioned by the National Institute for Health and Clinical Excellence). Long-acting reversible contraception: The effective and appropriate use of long-acting reversible contraception. October 2005. Available at: http://www.nice.org.uk/nicemedia/live/10974/29912/29912.pdf. Accessed Jun 19, 2010.
3. Organon Laboratories Ltd. Implanon 68mg implant for subdermal use: Summary of Product Characteristics (SPC). September 2009. Available at http://www.medicines.org.uk/EMC/medicine/5382/SPC/Implanon+68mg+implant+for+subdermal+use/ Accessed Jun 19, 2010.
4. The Information Centre for Health and Social Care. NHS Contraceptive services, England: 2004–2005 Available at: http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles/contraception/nhs contraceptive-services-england:-2004–2005. Accessed Jun 19, 2010.
5. The Information Centre for Health and Social Care. NHS Contraception Services, England: 2008–2009. Available at: http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles/contraception/nhs contraception-services-england:-2008–2009. Accessed Jun 19, 2010.
6. Data on file. Kenilworth, NJ: Schering Corporation. Available at: http://www.implanon-usa.com/HCP/aboutImplanon/index.asp. Accessed Jun 19, 2010.
7. Croxatto HB. Mechanisms that explain the contraceptive action of progestin implants for women. *Contraception*. 2002;65:21–27.
8. Huber J, Wenzl R. Pharmacokinetics of Implanon. An integrated analysis. *Contraception*. 1998;58:85S–90S.
9. Bennink HJ. The pharmacokinetics and pharmacodynamics of Implanon, a single- rod etonogestrel contraceptive implant. *Eur J Contracept Reprod Health Care*. 2000;5 Suppl 2:12–20.
10. Australian Adverse Drug Reactions Bulletin. 2007 Aug;26:4. Available at: http://www.tga.gov.au/adr/aadrb/aadr0708.htm. Accessed Jun 19, 2010.
11. Bensouda-Grimaldi L, Jonville-Bera AP, Beau-Salinas F, Llabres S, Autret-Leca E; Le Réseau des Centres Régionaux de Pharmacovigilance. [Insertion problems, removal problems, and contraception failures with Implanon]. *Gynecol, Obstet Fertil*. 2005;33:986–990. French.
12. Agrawal A, Robinson C. An assessment of the first 3 years' use of Implanon in Luton. *J Fam Plann Reprod Health Care*. 2005;31:310–312.
13. Flores JB, Balderas ML, Bonilla MC, Vazquez-Estrada L. Clinical experience and acceptability of the etonogestrel subdermal contraceptive implant. *Int J Gynaecol Obstet.* 2005;90:228–233.
14. Funk S, Miller MM, Mishell J, et al. Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. *Contraception*. 2005;71:319–326.
15. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (Apr 2005). Progestogen-only implants. Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceProgestogenOnlyImplantsApril08.pdf. Accessed Jun 19, 2010.
16. Back DJ, Bates M, Bowden A, et al. The interaction of phenobarbital and other anticonvulsants with oral contraceptive steroid therapy. *Contraception*. 1980;22:495–503.
17. Crawford P, Chadwick DJ, Martin C, Tjia J, Back DJ, Orme M. The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids. *Br J Clin Pharmacol.* 1990;30:892–896.
18. Fattore C, Cipolla G, Gatti G, et al. Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. *Epilepsia*. 1999;40:783–787.
19. Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia*. 1997;38:317–323.
20. British National Formulary. British Medical Association and the Royal Pharmaceutical Association of Great Britain: London, UK; 2010. Available at http://bnf.org/bnf/bnf/current/4552.htm. Accessed Jul 11, 2010.
21. Baciewicz AM, Chrisman CR, Finch CK, Self TH. Update on rifampin and rifabutin drug interactions. *Am J Med Sci*. 2008;335:126–136.
22. Barditch-Crovo P, Trapnell CB, Ette E, et al. The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive. *Clin Pharmacol Ther.* 1999;65:428–438.
23. Gupta KC, Ali MY. Failure of oral contraceptive with rifampicin. *Med J Zambia*. 1981;15:23.
24. Skolnick JL, Stoler BS, Katz DB, Anderson WH. Rifampin, oral contraceptives, and pregnancy. *JAMA*. 1976;236:1382.
25. Cote J. Interaction of griseofulvin and oral contraceptives. *J Am Acad Dermatol.* 1990;22:124–125.
26. Ouellet D, Hsu A, Qian J, et al. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *Br J Clin Pharmacol*. 1998;46:111–116.
27. Liverpool HIV Pharmacology Group (LHPG), University of Liverpool, Liverpool, UK. Available at: http://www.hiv-druginteractions.org. Accessed Jul 11, 2010.
28. Schindlbeck C, Janni W, Friese K. Failure of Implanon contraception in a patient taking carbamazepin for epilepsia. *Arch Gynecol Obstet*. 2006;273:255–256.
29. Patni S, Ebden P, Kevelighan E, Bibby J. Ectopic pregnancy with Implanon. *J Fam Plann Reprod Health Care*. 2006;32:115–116.
30. Mansour M, Louis-Sylvestre C, Paniel B-J. Ectopic pregnancy with etonogestrel contraceptive implant (Implanon): First case. *J Gynecol Obstet Biol Reprod (Paris)*. 2005;34:608–609. French.
31. Matiluko AA, Soundararjan L, Hogston P. Early contraceptive failure of Implanon in an HIV-seropositive patient on triple antiretroviral therapy with zidovudine, lamivudine and efavirenz. *J Fam Plann Reprod Health Care*. 2007;33:277–278.
32. Sanofi-aventis. Rifinah 150/100 mg and 300/150 mg. Summary of Product Characteristics (SPC) 2010. Electronic Medicines Compendium (eMC). Available at: http://www.medicines.org.uk/EMC/medicine/7494/SPC/Rifinah+150+100mg+and+300+150mg/#PRODUCTINFO. Accessed Jun 19, 2010.
33. Baxter K. Stockley's drug interactions. London: Pharmaceutical Press; 2008.