Optimizing subcutaneous injection of the gonadotropin-releasing hormone receptor antagonist degarelix

Jack Barkin, MD,[1] Shelley Burton, RN,[2] Carole Lambert, MD[3]

[1]Department of Surgery, University of Toronto, Toronto, Ontario, Canada

[2]Toronto Urology Clinical Study Group, Toronto, Ontario, Canada

[3]Department of Radiation Oncology, CHUM Notre Dame, Montreal, Quebec, Canada

BARKIN J, BURTON S, LAMBERT C. Optimizing the subcutaneous injection of the gonadotropin-releasing hormone receptor antagonist degarelix. *Can J Urol* 2016;23(1):8179-8183.

The gonadotropin-releasing hormone (GnRH) receptor antagonist degarelix has several unique characteristics compared to luteinizing hormone-releasing hormone (LHRH) analogs used in the management of prostate cancer. Notable differences of GnRH receptor antagonists include no flare reaction, and a more rapid suppression of testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and prostate-specific antigen (PSA) compared to LHRH analogs. Despite emerging evidence supporting the use of GnRH receptor antagonists over the more widely used LHRH analogs in the management of prostate cancer, physicians may be reluctant to prescribe degarelix. They may be concerned about patient complaints about injection-site reactions (ISRs). The subcutaneous injection of degarelix has been associated with a higher rate of ISRs compared with the intramuscular injections of LHRH analogs. This "How I Do It" article describes techniques and strategies that have been developed by physicians and nurses to reduce the discomfort associated with the subcutaneous delivery of degarelix.

Key Words: GnRH receptor antagonists, side effects, injection site reactions, subcutaneous injection technique

Introduction

Degarelix is a selective gonadotropin-releasing hormone (GnRH) receptor antagonist (blocker) that competitively and reversibly binds to GnRH receptors in the pituitary. This results in a rapid reduction in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thus reducing secretion of testosterone by the testes. Degarelix is indicated for testosterone suppression in patients with advanced hormone-dependent prostate cancer in whom androgen deprivation is warranted.

Degarelix (Firmagon) was approved by the US Food and Drug Administration (FDA) in 2008 and by Health Canada in 2009. As standard care, the starting dose of degarelix is 240 mg, which is given as two separate subcutaneous injections of 120 mg at a concentration of 40 mg/mL, injected into alternate sides of the

Accepted for publication December 2015

Address correspondence to Dr. Jack Barkin, Department of Surgery, University of Toronto, 404-960 Lawrence Avenue West, Toronto, ON M6A 3B5 Canada

abdomen. The initial dose is followed by a monthly maintenance dose of 80 mg given as one subcutaneous injection at a concentration of 20 mg/mL.[1]

With a GnRH receptor antagonist there is no flare reaction and a more rapid suppression of testosterone, LH, FSH, and prostate-specific antigen (PSA) compared to an LHRH analog such as leuprolide.[2,3] There have also been reports that compared to commonly used LHRH analogs, degarelix is associated with a lower risk of cardiac events, particularly in men with pre-existing cardiovascular disease.[4] Studies have also reported that over a 1-year period, there was a clinically significant increase in PSA progression-free survival with degarelix compared to LHRH analogs.[5]

Despite the potential benefits of GnRH receptor antagonists over LHRH analogs in the management of prostate cancer, physicians are often reluctant to prescribe degarelix. Patients may complain about injection-site reactions (ISRs). Subcutaneous injection of degarelix has been reported to be associated with a higher incidence of ISRs compared with intramuscular injection of the LHRH analog leuprolide (40% versus < 1%; $p < 0.001$, respectively).[2] Since degarelix is administered monthly, the potential for ISRs is a significant concern.

The most common degarelix treatment-related adverse events (AEs) experienced by patients are related to ISRs. These ISRs included pain, erythema, swelling, and nodules (in 31%, 21%, 8%, and 7% of patients, respectively).[6] Most reactions occurred after the first injection; 31% of 276 degarelix 240 mg initiation doses were reported to be associated with ISRs. The incidence decreased for subsequent doses; 2.5% of 9142 maintenance doses of 80 mg degarelix were associated with a reaction. In total, 12 of 544 patients (2%) treated with degarelix discontinued treatment because of ISRs. While administration of subsequent doses of degarelix after the initial dose may be associated with a decline in ISRs, and treatment discontinuation is low, it is still desirable to develop subcutaneous injection techniques to minimize ISRs including pain, while allowing for the desired clinical effect.

Key causes of ISRs involving degarelix administration include suboptimal injection location, mechanical injury to the surrounding tissue, and contact between the peptide and the dermis. The local effect appears to be an inflammatory response that results in macrophage infiltration and granuloma formation. Thus, to prevent pain and local side effects, better injection strategies should cover injection-site selection, patient positioning, speed and timing of the injections, and the use of certain drug administration techniques, notably those that limit the amount of drug that is in contact with the skin. One very important way to help mitigate injection-site discomfort is to explain the subcutaneous injection procedure to patients before the injection, thereby reducing potential anxiety.[7]

Degarelix self-forming depot and timing of administration

Degarelix is supplied as a powder, and once it is reconstituted with water the degarelix molecules aggregate and cross-link in a gel-forming network, resulting in a hydrogel. Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 2 hours after addition of a solvent.[1] While the depot-forming process progresses relatively slowly in aqueous media, it takes place almost instantly in the interstitial environment after subcutaneous injection. Once reconstituted, the product should be administered immediately.

Basic instructions for degarelix administration

According to the prescribing information, degarelix should be injected deeply subcutaneously in the abdominal region, avoiding an intradermal administration and rotating through all four quadrants of the anterior abdominal wall (see prescribing information for more details).[1] As with other drugs that are administered by subcutaneous injection, the injection site should be varied periodically. Injections should be given in areas of the body where the patient will not be exposed to pressure; thus sites that are not close to the waistband, belt area, or ribs are preferred.[1] To be effective, medications administered using the subcutaneous route should be delivered into the subcutaneous adipose tissue and not into the dermis or muscle. Degarelix administration is limited to the abdomen, unlike other drugs that can be subcutaneously injected into the abdominal region, the lateral aspects of the upper arms and thighs, or the back and lower loins.[7]

The abdomen is the site of choice for degarelix injection, since the skin in this region has a thicker subcutaneous tissue,[7] which might reduce the risk of extravasation of the injected drug into the superficial tissue plane.[8,9] Cool compresses can induce vasoconstriction at the injection site, and slow the blood flow and metabolism and mitigate the inflammatory process with local physiological effects, thus decreasing the incidence of pain and discomfort,[9] although not necessarily decreasing the frequency or size of bruising.[10,11]

TABLE 1. **The recommended injection technique for degarelix**

- Gently grasp the patient's abdominal skin between your thumb and forefinger; elevate the subcutaneous tissue, and hold it firmly.
- Insert the needle into the patient's skin that is between your thumb and forefinger; inject it deeply at an angle of not less than 45 degrees. The best angle is 90 degrees, to ensure deeper penetration through the dermis, thus reducing exposure to the peptide.
- Gently pull back the plunger to check if blood is aspirated. If blood appears in the syringe, the medicinal product can no longer be used; discontinue the injection procedure and discard the syringe and needle (and then reconstitute a new dose for the patient).
- Inject degarelix slowly.
- After injection, remove the needle, keeping the syringe at the same angle.
- Put pressure on the injection site for about 10 seconds. (Do not rub).

As with other injectable drugs, aseptic injection techniques should be used. Gloves should be worn during drug preparation and administration. The recommended injection technique for the administration of degarelix is described in Table 1.[1]

General suggestions to minimize ISRs

ISRs can be minimized if injections are administered by an experienced health care professional, and applying a cold gauze compress may provide relief if a reaction does occur. Choosing an injection site that is a good distance from the belt line is important, because if an ISR is created on the lower quadrants of the abdomen just above the belt line, further pressure will be created with sitting or bending. Administration of degarelix to patients in a supine position increases the control of the delivery of the drug (i.e. there is increased steadiness of both the patient and the health care provider's hand) especially during slow delivery and with other combined techniques described below. Studies have shown that slow administration of a subcutaneous injection reduces the extent of bruising and the intensity of pain at the injection site. This might be due to the fact that a slower injection reduces the pressure in the injection site, thereby decreasing tissue trauma.[12]

"How I Do It" from a nurse's perspective

Nurses who have experience with subcutaneous injection of degarelix use a number of simple techniques, individually or in combination, which minimize the amount of drug that is in contact with the dermis, thus reducing the risk of ISRs. Techniques that can be used to inject potentially irritating substances are the air bubble techniques (the back bubble, front bubble, and air sandwich or double bubble techniques), the Z-track technique, and the delayed withdrawal of the needle post-injection (the 30-second rule) technique, listed in Table 2.

Data about the use of these techniques to inject degarelix in 231 patients was collected in a survey conducted in 25 centers across Canada (unpublished data from Ferring). This survey, which explored best practices that were used to optimize subcutaneous delivery of degarelix, showed that combined injection techniques were being used in 51% of patients. Among the single techniques, the "30-second rule" was used

TABLE 2. **Techniques used by nurses to reduce injection site reactions associated with degarelix**

1. The air bubble techniques
    a. Back bubble
    b. Front bubble
    c. Air sandwich or double bubble
2. Z-track technique
3. 30 second rule: delayed withdraw of the needle post-injection

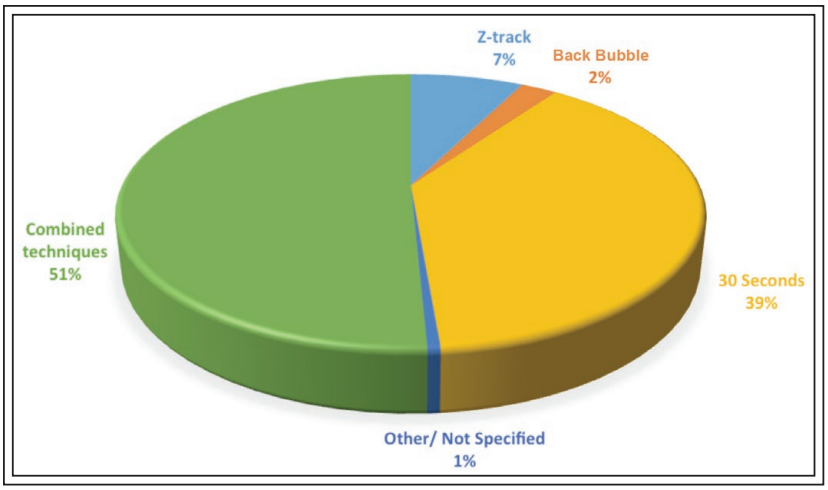

Figure 1. Combined versus single injection techniques for degarelix (n = 231).

most frequently, Figure 1. Looking at single and combined techniques for subcutaneous injection of degarelix, the 30-second rule was part of the technique in 68% of cases, followed by the Z-track technique (55%) and the back bubble technique (39%).

Back bubble technique

The back bubble technique involves leaving a small air space in the syringe (at the head of the plunger). In this method, up to 0.2 mL to 0.3 mL of air is left in the injector (airlock) and first the entire drug and then second, air is delivered into the subcutaneous tissue during injection.[9,13] The rationale for the back bubble technique is to create a break in the injection track and seal off the drug below, to assist in depot formation, and minimize back tracking and drug contact with the dermis.

Front bubble technique

After the reconstituted contents of the vial have been drawn up into the syringe and a dry needle is attached to the syringe, an air space (front bubble) occurs within the shaft of the needle.[14] This is easily achieved by not pushing the drug into the needle shaft. A drug-free needle shaft (i.e. containing air only) minimizes loss of medicinal product from the syringe during injection and ensures that no peptide will come in contact with the dermis upon insertion into the injection site.

Double bubble technique

The air sandwich or double bubble technique is recommended as a subcutaneous injection strategy to avoid seeding of irritating medication in the injection track and to reduce ISRs.[14] The double bubble

TABLE 3. **Z track technique for subcutaneous injection (adapted from use for intramuscular injection)**

- Using your non-dominant hand, displace the patient's skin and subcutaneous tissue by pulling the skin laterally or downward from the injection site.
- Holding the skin firmly, quickly and smoothly insert the needle at an angle of not less than 45 degrees at the spot where your finger was initially placed before displacing the skin laterally.
- Continue to hold the skin firmly with your non-dominant hand.
- With your dominant hand, aspirate with the syringe for 5 to 10 seconds.
- If no blood returns with aspiration, slowly inject the medication (at a rate of 10 seconds/mL). If you see blood in the syringe, withdraw the needle, properly discard the medication and syringe, and prepare another dose for injection.
- Once the drug is completely injected, wait 10 seconds before withdrawing the needle to allow the medication to disperse evenly in the tissue.
- Withdraw the needle with a smooth, steady motion at the same angle it was inserted.
- Release the skin to its original position to create a zigzag needle path. By sliding of the tissue planes across each other, the escape of medication from the injection site is prevented.
- Using dry gauze, apply very gentle pressure to the puncture site.
- Never massage the Z-track injection site, since this may cause irritation.
- Assess the injection site for complications and check it again in 2 to 4 hours, if possible.
- Instruct the patient to not wear tight or constricting clothing, because this can force out the injected medication.

technique is a combination of the front and back bubble as described in this article – i.e. an air bubble behind the medication (at the plunger end of the syringe) and a dry needle only containing air. (Do not expel the air in the needle before doing the injection) The drug is injected subcutaneously.

The Z-track technique

Similar to the back bubble technique, the Z-track technique[13] is intended to minimize back-leak through the puncture channel.[15] It is typically recommended for use with intramuscular injections and can be adapted for subcutaneous medications as it is believed to reduce pain and virtually eliminate the risk of medication leaking back into the needle track.[16]

With the Z-track technique, the skin and the subcutaneous tissue are displaced laterally before the needle is inserted, which moves the cutaneous and subcutaneous tissues by 1 cm to 2 cm. The needle is then inserted and the injection is given. Once the needle is removed, the tissue is restored to its normal position, sealing off the needle track and preventing leakage at the injection site. The Z-track technique is described in Table 3.[13,15]

Delayed withdraw of the needle post-injection (the 30-second rule)

With this technique, after the degarelix is injected, the needle is left in place at least 30 seconds, to allow a gel matrix depot to form. By allowing the degarelix to form a matrix, this minimizes the amount of drug tracking back on the needle path and coming in contact with the dermis. Singing the "Happy Birthday" song silently is the appropriate delay time. If sung aloud, this would certainly distract the patient!

Conclusion

These subcutaneous injection techniques (front bubble, back bubble, Z-track and 30-second rule) used alone or in combination, allow for better depot formation, minimize drug contact with the more sensitive cutaneous layer, and minimize the back-leak through the puncture site. If properly used, these techniques will likely improve patient satisfaction and compliance, while optimizing full drug delivery. □

References

1. Ferring Pharmaceuticals, Firmagon (degarelix for injection) Prescribing Information, Revised 03/2015 (Available at http://www.firmagon.us/assets/full_pi-2cf8bc4f2d7216ec431b83f29b875150.pdf.pdf
2. Klotz L, Boccon-Gibod L, Shore ND et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008;102(11):1531-1538.
3. Boccon-Gibod L, Iversen P, Persson BE. Degarelix 240/80 mg: a new treatment option for patients with advanced prostate cancer. *Expert Rev Anticancer Ther* 2009;9(12):1737-1743.
4. Barkin J. Risks, benefits and approaches to hormonal blockade in prostate cancer. Highlights from the European Urology Association (EUA) Meeting 2015. *Can J Urol* 2015;22(3):7847-7852.
5. Tombal B, Miller K, Boccon-Gibod L et al. Additional analysis of the secondary endpoint of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. *Eur Urol* 2010;57(5):836-842.
6. Crawford ED, Shore ND, Moul JW et al. Long-term tolerability and efficacy of degarelix: 5-year results from a phase III extension trial with a 1-arm crossover from leuprolide to degarelix. *Urology* 2014;83(5):1122-1128.
7. Hunter J. Subcutaneous injection technique. *Nursing Standard* 2008;22(21):44.
8. Michell GS. Pauszek M. Effect of injectate volume on local hematoma formation during low-dose heparin therapy. *Crit Care Med* 1987;15:87-88.
9. Avşar G, Kaşikçi M. Assessment of four different methods in subcutaneous heparin applications with regard to causing bruise and pain. *Int J Nurs Pract* 2013;19(4):402-408.
10. Ross S, Soltes D. Heparin and hematoma: does ice make a difference? *J Adv Nurs* 1995;21(3):434-439.
11. Kuzu N, Ucar H. The effect of cold on the occurrence of bruising, haematoma and pain at the injection site in subcutaneous low molecular weight heparin. *Int J Nurs Stud* 2001;38(1):51-59.
12. Dadaeen A, Bahreini M, Bazi P, Ostovar A, Raeisi A, Dobaradaran S. The effect of duration of subcutaneous injection on the extent of bruising and pain intensity at injection sites among patients receiving enoxaparin sodium: a randomized self-controlled clinical trial. *Int Cardiovasc Res J* 2015;9(2):77-82.
13. Workman B. Safe injection techniques. *Nursing Standard* 1999; 13(39):47-53.
14. Kurtin S, Knop CS, Milliron T. Subcutaneous administration of bortezomib: strategies to reduce injection site reactions. *J Adv Pract Oncol* 2012;3(6):406-410.
15. Pullen RL. Administering medication by the Z-track method. *Nursing* 2005;35(7):24
16. Beyea SC, Nicoll LH. Administration of medications via the intramuscular route: an integrative review of the literature and research-based protocol for the procedure. *Appl Nurs Res* 1995; 8(1):23-33.