Injection-Site Nodules Associated With Once-Weekly Subcutaneous Administration of Semaglutide

Elizabeth B. Hearn and Justin J. Sherman

University of Mississippi School of Pharmacy, Jackson, MS

Glucagon-like peptide 1 (GLP-1) receptor agonists are a safe and effective treatment option for patients with type 2 diabetes (1). Selective activation of the GLP-1 receptor causes glucose-dependent insulin secretion, resulting in a very low risk of hypoglycemia (2). The additional mechanism of slowing gastric emptying has resulted in reliable weight loss with this class of antihyperglycemic medications (3). In addition, multiple agents in this drug class (semaglutide, liraglutide, and dulaglutide) have been proven to reduce the risk of cardiovascular events (4).

Furthermore, the possibility of once-weekly dosing for glycemic control in type 2 diabetes has been realized with some GLP-1 receptor agonists (semaglutide, exenatide extended-release, and dulaglutide) as a result of albumin binding that decreases renal clearance and protects against metabolic degradation by the dipeptidyl peptidase-4 enzyme (2). Poor adherence to pharmacologic therapy is well documented in patients with type 2 diabetes and is linked to inadequate glycemic control (based on the American Diabetes Association's general A1C goal of <7%), and once-weekly dosing has been shown to improve adherence rates (5,6).

The use of GLP-1 receptor agonists in practice has become more prominent in recent years, and adverse reactions are generally benign. Most commonly, patients have reported gastrointestinal upset (>10%) and injection-site reactions (>1%) (1,7).

General injection-site reactions (e.g., erythema, pain, or rash) have been reported with all of the commercially available GLP-1 receptor agonists (i.e., exenatide, lixisenatide, liraglutide, dulaglutide, and semaglutide) (8–13). However, post-marketing reports have revealed that exenatide extended-release, specifically, may cause more alarming injection-site reactions (8,14). During clinical trials, small, asymptomatic, quickly-resolving injection-site nodules were reported by 17.1% of exenatide extended-release users and 12.7% of exenatide users (7,14). Seven years after approval of exenatide extended-release by the U.S. Food and Drug Administration (FDA), a post-marketing review of the FDA's Adverse Event Reporting System (FAERS) by Jones et al. (14) found 27 reports of injection-site nodules with exenatide extended-release use between 2012 and 2013, with 15 patients (55.5%) reporting nodules that did not resolve over time, even after discontinuation of exenatide extended-release injections (14). These injection-site nodules were described as "hard, subcutaneous lumps, masses, or indurations," and the most common reports included skin discoloration, pain, pruritus, warmth, and swelling at injection sites. In addition, the DURATION-6 trial found that injection-site nodules occurred in 10% of patients treated with exenatide extended-release (15). There have also been case reports of suspected exenatide extended-release–induced injection-site granuloma, which spiked concerns about the long-term safety of exenatide extended-release use (14).

Because of the post-marketing concerns about long-term risks associated with these injection-site reactions, the package insert for exenatide extended-release now features a precautionary warning about abscess, cellulitis, necrosis, surgical intervention, and subcutaneous nodules (8).

Aside from exenatide extended-release, the risk of injection-site nodules is small for all other GLP-1 receptor agonists on the market. Until now, there have been no reports of injection-site nodules associated with semaglutide once-weekly injections (13). The purpose of this report is to highlight a novel injection-site nodule reaction observed in a patient using once-weekly semaglutide injections.

Corresponding author: Elizabeth B. Hearn, elizabethbellhearn@gmail.com

https://doi.org/10.2337/ds20-0033

TABLE 1 Naranjo Adverse Drug Reaction Probability Scale (16)

Question	Yes	No	Do Not Know	Score*
Are there previous conclusive reports on this reaction?	+1	0	0	0
Did the adverse reaction appear after the suspected drug was administered?	+2	−1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	+2
Are there alternative causes (other than the drug) that could on their own have caused this reaction?	−1	+2	0	+2
Did the reaction reappear when a placebo was given?	−1	+1	0	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	+1
Did the patient have a similar reaction to the same drug or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse reaction confirmed by any objective evidence?	+1	0	0	+1
TOTAL SCORE:				**9**

*Scale interpretation: definite if score is ≥9, probable if score is 5–8, possible if score is 1–4, and doubtful if score is 0 (16).

Case Presentation

A 75-year-old man was started on semaglutide 0.25 mg once-weekly subcutaneous injection in June 2019 and was appropriately titrated to 0.5 mg once weekly after 4 weeks. His A1C decreased from 7.1% in June 2019 to 6.3% in September 2019. The patient voiced no adverse reactions, complaints, or concerns at that time, so the semaglutide dose was maximized to 1 mg once weekly in September 2019. Nine days later, the patient complained of a "bubble" on his left abdomen at the site of the injection. The patient reported injecting in the same location each week, so he was educated on the importance of rotating injection sites. The patient voiced his understanding that rotating injection sites reduces the risk of lipohypertrophy that could impair medication absorption and increase glycemic variability (1).

The following week, the patient reported adherence to rotating the injection site and stated that a new nodule formed at the injection site on his right abdomen. The patient demonstrated his injection technique during the appointment, and no issues were identified. The 1-mg dose of once-weekly subcutaneous semaglutide was continued, and proper injection technique and rotation of sites was reinforced.

In October 2019, the patient reported still experiencing injection-site nodules on his abdomen after each weekly injection. The nodules were observed by the ambulatory care pharmacist conducting the patient interview. The nodules were quarter-sized, hard, erythematous, pruritic, and raised, appearing within minutes of injection and typically disappearing within 2–4 days. The patient denied pain or tenderness to touch, and the dose was decreased back to 0.5 mg semaglutide subcutaneously once weekly.

The patient returned to the clinic 4 weeks later, in November 2019, and reported that the nodules were still occurring. Nodules were visible to the pharmacist, with the same size, shape, and coloring as those reported after administration of 1-mg doses. However, the nodules associated with the 0.5-mg dose typically subsided within 24 hours (as opposed to 2–4 days with 1 mg).

The patient was instructed to stop semaglutide and start dulaglutide once-weekly subcutaneous injections. No nodules have been reported in the 5 months since the patient stopped semaglutide and started dulaglutide. The patient reports injecting the dulaglutide using the same technique as previously used with semaglutide, and the dulaglutide has been well tolerated with no adverse reactions.

Discussion

To our knowledge, this is the first reported case of injection-site nodules associated with semaglutide (13). Although other injection-site reactions have been reported to FAERS, this specific adverse reaction has not been reported until this case (13).

The team of pharmacists used the Naranjo Adverse Drug Reaction Probability Scale (Table 1) to discern that these patient-reported nodules are a definite result of semaglutide subcutaneous injection (16). There is no evidence that injection-site nodules are a class-wide adverse reaction seen across all GLP-1 receptor agonists. Also, there is no clear mechanism to explain what causes the nodules associated with exenatide extended-release (14). Hypotheses for the reaction include anti-exenatide antibody response, eosinophilic response, inflammatory foreign body reaction, or subcutaneous reaction from the microsphere excipient in the exenatide extended-release formulation (14,17).

Based on the description of adverse reactions with exenatide extended-release described by Jones et al. (14), the injection-site nodules with semaglutide described in this case report align with the description of those seen with exenatide extended-release (14). The patient did not experience nodules until reaching the appropriately titrated maximum dose 6 weeks after therapy initiation; this delay in adverse reaction supports the antibody or eosinophilic response hypotheses, which occur most commonly after multiple exposures over time.

This patient's injection-site nodules may be the first adverse reaction of its kind for subcutaneous semaglutide. This report should encourage clinicians to consider that novel adverse reactions should be thoughtfully and thoroughly reported.

Conclusion

Post-marketing reports of injection-site nodules led to inclusion of a precautionary warning in the exenatide extended-release package insert (8). This reaction was not previously reported for once-weekly semaglutide, but the risk of injection-site nodules cannot be ruled out. Further FAERS reports or patient case reports are needed to confirm the adverse reaction for semaglutide described in this patient case.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

E.B.H. wrote the manuscript and researched data. J.J.S. reviewed/edited the manuscript and contributed to discussion. E.B.H. is the guarantor of this work and takes responsibility for the integrity of the data presented and the accuracy of the case report.

REFERENCES

1. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S98–S110
2. Hinnen D. Glucagon-like peptide 1 receptor agonists for type 2 diabetes. Diabetes Spectr 2017;30:202–210
3. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol 1997;273:E981–E988
4. American Diabetes Association. 10. Cardiovascular disease and risk management: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S111–S134
5. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence 2016;10:1299–1307
6. Iglay K, Cao X, Mavros P, Joshi K, Yu S, Tunceli K. Systematic literature review and meta-analysis of medication adherence with once-weekly versus once-daily therapy. Clin Ther 2015;37:1813–21.e1
7. Filippatos TD, Panagiotopoulou TV, Elisaf MS. Adverse effects of GLP-1 receptor agonists. Rev Diabet Stud 2014;11:202–230
8. Exenatide [package insert]. Wilmington, DE, AstraZeneca Pharmaceuticals, 2018
9. Lixisenatide [package insert]. Bridgewater, NJ, Sanofi U.S., 2016
10. Liraglutide [package insert]. Princeton, NJ, Novo Nordisk, 2010
11. Dulaglutide [package insert]. Indianapolis, IN, Eli Lilly, 2017
12. Semaglutide [package insert]. Plainsboro, NJ, Novo Nordisk, 2017
13. U.S. Food and Drug Administration. FDA adverse event reporting system public dashboard. Available from https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. Accessed 23 March 2020
14. Jones SC, Ryan DL, Pratt VSW, Niak A, Brinker AD. Injection-site nodules associated with the use of exenatide extended-release reported to the U.S. Food and Drug Administration adverse event reporting system. Diabetes Spectr 2015;28:283–288
15. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013;381:117–124
16. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–245
17. Riswold K, Flynn V. Persistent injection site nodules from exenatide: successful treatment with intralesional triamcinolone. JAAD Case Rep 2018;4:830–832