Systemic Allergic Reaction to the GLP-I Receptor Agonist Exenatide

Journal of Pharmacy Technology
2014, Vol. 30(5) 182–186
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DOI: 10.1177/8755122514539462
pharmatech.sagepub.com

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Abstract

Objective: To report a case of systemic hypersensitivity to the glucagon-like peptide-I (GLP-I) receptor agonist exenatide used in diabetes care to provide significant information within the context of postmarketing safety surveillance of this new drug class. **Case Summary:** We report on a 52-year-old male with insufficiently controlled diabetes. GLP-I agonist treatment was indicated and the patient was started on 5 to 10 µg exenatide (Byetta) twice daily, which had to be stopped after 1 month due to intolerable nausea. One year later, an attempt with 0.6 to 1.8 mg liraglutide (Victoza) once daily was well tolerated but lacked efficacy after a few months. Finally, the patient was started on 2 mg exenatide (Bydureon) once weekly. Concomitant treatment included metformine 1000 mg twice daily and candesartan/hydrochlorothiazide (Blopess Plus) 16/12.5 mg once daily. A few hours after the second injection, local urticaria and disseminated pruritus evolved and after the third injection pruritus, urticaria, and shortness of breath developed, which resolved to antihistamines and corticosteroids. Intradermal tests were positive for Byetta (1:1000) and Bydureon (1:100) (both exenatide), while Victoza (liraglutide) was negative (1:10). Specific immunoglobulin E (IgE) to the drugs was not available for testing. **Discussion:** An objective causality assessment revealed that the adverse effect to exenatide (Bydureon) was probable (Naranjo probability scale: score of 8). Consistency was established through positive skin tests and the biological explanation that the administration of GLP-I receptor agonists has been associated with antibody formation. **Conclusion:** Considering emerging use of GLP-I receptor agonists, systemic hypersensitivity should be recognized as a risk in clinical practice.

Keywords

allergy, hypersensitivity, exenatide, skin tests, GLP-I receptor agonist, adverse reaction, allergic reaction, postmarketing surveillance

Background

The incidence of type 2 diabetes is rising worldwide. The increasing prevalence of obesity is an important risk factor. Other underlying mechanisms of abnormal β -cell function may be more complex including not only environmental factors but also different mechanisms such as genetic susceptibility. In diabetic patients, relative insulin deficiency is caused by insulin resistance in different tissues such as muscle and fat cells and excessive glucagon secretion.¹ Furthermore, the reduction of responsiveness to 2 incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), plays a role.¹

A variety of therapeutic options are available for diabetes. When initial treatment with diet, lifestyle changes and metformin does not suffice an add-on therapy to metformin becomes necessary for most patients. Which agent should be combined with metformin still remains unclear. While therapies with sulphonylurea (SU), insulin, and thiazolidinediones (TZD) are widely used, control of diabetes is not always achieved.² Furthermore, side effects such as

hypoglycemia are frequently observed in the application of insulin or SU.² Weight gain is an important side effect of insulin, SU, and TZD therapy.² Increased fracture rate with TZD and gastrointestinal disturbances with metformin are the most frequent adverse effects and may cause limitation of treatment.² In order to optimize therapy for diabetes, new drugs have been developed to achieve both better control of diabetes and reduction of adverse reactions. Newer drugs such as dipeptidyl peptidase-4 (DPP-4) inhibitors improve insulin secretion and inhibit glucagon release but do not have clinically relevant effects on gastric emptying, appetite, or weight.³

Lately other incretin-based therapies, such as GLP-1 receptor agonists, have come into focus through their

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working mechanism that not only improves glycemic control but also facilitates weight loss.⁴ This may have a positive effect on frequent comorbidities in diabetes. In fact one study has been conducted evaluating the positive effect on patients with adipositas only, potentially expanding the indication spectrum for this new drug class (see also clinicaltrials.gov NCT00781937). The very short plasma half-life of native GLP-1 peptide, due to rapid inactivation by the protease-DPP-4 and by renal clearance, reduces the clinical potential of the native peptide.⁵ The effectiveness of GLP-1 receptor agonists for the treatment of diabetes type 2 thus required a continuous application of these agents via infusion or repeated injections and prompted the development of new drugs with longer action.

Currently, 2 GLP-1 receptor agonists for subcutaneous (sc) use are on the market. Exenatide is available either for twice daily (bid) (Byetta) or once weekly (qwk) (Bydureon), and liraglutide (Victoza) is available for once daily (qd) application. Liraglutide is a DPP-4-resistant fatty acylated GLP-1 molecule that binds noncovalently to serum albumin and exhibits more potent and sustained glucose-lowering effects compared to GLP-1.⁶ With a half-life of about 13 hours, a once daily sc administration suffices.⁷ Liraglutide treatment is initiated with 0.6 mg once daily, increased to 1.2 mg after 1 week, and sometimes increased to up to 1.8 mg.⁷

Exenatide (exendin-4) is a DPP-4-resistant GLP-1 receptor agonist enhancing the expression of key genes, glucose-dependent insulin secretion, suppression of glucagon secretion, and slowing down gastric emptying.⁸ Exenatide (Byetta) has a half-life of 2.5 hours and has to be given twice daily. As it is given in micrograms, treatment is started with 5 µg and increased to 10 µg after 4 weeks if possible.⁷ Exenatide once weekly formulation (Bydureon) has been developed using biodegradable polymeric microspheres that entrap exenatide.⁹ It is incorporated into a specific biomaterial, a matrix of poly(D,L-lactide-co-glycidic) (PLG), and with this extended release preparation a gradual drug delivery at controlled rates is achieved.¹⁰ Eliminated via the kidneys, a stable plasma level is obtained after 5 to 10 weeks of sc injection of 2 mg exenatide qw, comparable to the peak concentrations in exenatide bid.⁹

The most common adverse events are gastrointestinal symptoms such as diarrhea, nausea, and vomiting.⁴ They are considered to be a class effect of GLP-1 receptor agonists and may often be overcome after a few injections. In the LEAD-6 trial in which liraglutide qd was compared to exenatide bid, gastrointestinal side effects were most pronounced with exenatide bid compared to liraglutide qd with 28% having nausea and 9.9% vomiting compared with 25.5% and 6.0%, respectively.¹¹ After 8 to 10 weeks, the percentage of patients that reported nausea with liraglutide was below 10%, while in the exenatide group it remained at about 10%.¹¹ This was reduced even further after 26 weeks.¹¹ In the DURATION-1 trial, comparing exenatide

qwk to bid, the incidence of nausea (26% vs 35%) and vomiting (11% vs 19%) was lower in the exenatide qwk group compared to the exenatide bid group.¹² An explanation for the different incidence rates of gastrointestinal side effects dependent on the application frequency may be found in a tachyphylaxis that may occur when a continuous exposure with GLP-1 agonist is present, which is the case in the liraglutide qd and exenatide qwk groups.¹³ Other adverse events such as headaches,¹¹ pancreatitis, and thyroid disorders have been reported in a small number of cases.¹⁴ In the LEAD-6 trial about 7% of patients receiving exenatide reported unspecified skin and subcutaneous tissue disorders in comparison to 3% of patients receiving liraglutide.¹¹ In a meta-analysis including >5000 patients on exenatide bid only a subset of patients had an increase of immune-related adverse events, such as local injection site reactions and local urticaria.¹⁵ Generally, the treatment was considered to be safe and well tolerated without reports on systemic hypersensitivity reactions.¹⁵

Case Report

We report on a 52-year-old male Caucasian patient who had an established diagnosis of diabetes mellitus type 2 diagnosed 6 years earlier. Further known comorbidities were obesity (body mass index [BMI] 36.3 kg/m²), arterial hypertension, obstructive sleep apnea syndrome (OSAS), nonalcoholic steatohepatitis (NASH), lumbal cervical pain syndrome, and depression. Because of insufficient glycemic control with oral antidiabetic drugs and desired weight reduction, the patient qualified for GLP-1-receptor agonist therapy. In 2009, he first received 5 µg sc exenatide (Byetta) bid, which was increased to 10 µg sc exenatide bid after 1 month. This had to be stopped shortly after 1 month because of intolerable nausea. In October 2010, an attempt with 0.6 mg sc liraglutide (Victoza) was initiated, which was well tolerated also after the dosage increased to 1.8 mg sc but was suspended because of insufficient effects after a few months. In August 2012, the patient was started on 2 mg sc exenatide (Bydureon) with once weekly administration. The glycated hemoglobin (HbA1c) at that time was 7.2%. Concomitant treatment included Metformin 1000 mg bid, and Candesartan/Hydrochlorothiazide (Blosser Plus) 16/12.5 mg qd. In contrast to exenatide treatment 3 years ago, no gastrointestinal effects presented. Some hours after the second injection though, local injection site urticaria and disseminated pruritus developed. The patient at that point did not seek medical advice but after resolution of symptoms continued his treatment. After the third injection, a generalized pruritus, urticarial rash, throat itching, and shortness of breath appeared after a few hours. This time the patient presented immediately to his treating diabetologist and symptoms resolved after application of oral antihistamines and corticosteroids. Treatment with exenatide was

discontinued while concomitant medications remained unchanged and symptoms did not reappear.

Further personal history revealed that the patient was a self-employed dental-technician, drunk alcohol rarely, and was a current cigarette smoker with cumulative 40 pack years. His maternal grandmother had diabetes mellitus 2. Allergological evaluation revealed no history of allergic disorders, atopic diseases, or drug hypersensitivity. Before the above-described reaction no food intake or concomitant medication took place.

Oral and written informed consent was obtained. Skin prick tests were negative for liraglutide (Victoza) and Bydureon and questionable for Byetta, both exenatide. Intradermal tests were performed in a 1:10 dilution series, showing positive results for Byetta (1:1000) and Bydureon (1:100) (both exenatide), while Victoza (liraglutide) was negative in a solution of up to 1:10. Laboratory results were normal for total immunoglobulin E (IgE), mast cell tryptase, complement factor concentration, and activity. There were no other abnormal laboratory findings. Determination of specific antibodies to exenatide was not available. Experimental basophil activation test with exenatide (Bydureon) was negative in the patient, who was a nonreleaser to anti-IgE-receptor agonists and formyl-methionyl-leucyl-phenylalanine. To control for nonspecific test results, skin tests were performed on 2 patients under exenatide treatment and 2 healthy, unexposed controls. One patient was on treatment with Bydureon and the second patient on treatment with Byetta, both exenatide. Both patients had tolerated their medication well without adverse events. The 2 unexposed healthy controls did not have regular treatment. All 4 had negative intradermal tests with both exenatide preparations (Bydureon, Byetta) and liraglutide (Victoza) up to 1:10 dilutions. Experimental basophil activation tests with exenatide (Bydureon) were performed on all 4 volunteers showing negative test results.

In our patient, a diagnosis of a systemic immediate type allergic reaction to exenatide, possibly mediated by IgE, was retained and reported to the appropriate pharmacovigilance organization.

Discussion

Diabetes mellitus type 2 is a major health care problem and new therapeutics are required for patients with lacking glycemic control. New drug classes such as GLP-1 receptor agonists are emerging in diabetes care and with their positive effect on weight reduction the indication spectrum may expand even further. We report on a patient with a probable systemic hypersensitivity reaction to exenatide (Bydureon).

Originally discovered in Gila monster saliva, the active ingredient in exenatide is a 39-amino-acid synthetic version of exendin-4, a peptide that shares only 53% amino acid homology with human GLP-1.¹⁶ Liraglutide, on the other hand, is 97% identical to the native hormone.⁷

The concentration of liraglutide is much higher compared to exenatide, but the fraction of the hormone that is not bound to albumin is very low, probably leading to a similar concentration of free hormone in both medications.⁷ As for the large depot of bound liraglutide, its concentration does not vary much throughout the day and allows a variation in injection timing. The concentration of exenatide, on the other hand, varies from very low to therapeutic levels throughout the day.¹⁷

Consistent with the potentially immunogenic properties of therapeutic proteins, the administration of GLP-1 receptor agonists is often associated with antibody formation (IgG > IgM > IgA). Furthermore, as GLP-1 inhibitors can prolong actions of certain neuropeptides and chemokines, there is a possibility of allergic reactions occurring.¹⁸ As neither mice nor humans contain a gene encoding for an exendin-4-related peptide,¹⁶ exendin-4 is recognized as a foreign peptide by the immune system.¹⁹ In a mouse model, the exposure with exendin-4 has been shown to lead to an activation of humoral and cellular immune responses.¹⁹ In human diabetic subjects treated with twice daily exenatide, development of anti-exendin-4 antibodies occurred in 41% to 49% of treated patients after 30 weeks of therapy.²⁰

The incidence of antibody formation to exenatide appears to be more frequent in patients on exenatide in comparison to patients receiving liraglutide.⁴ In the LEAD-6 study, liraglutide qd was less immunogenic than exenatide bid, less than 10% of liraglutide-treated patients developed antibodies to liraglutide, and no apparent effect on efficacy was shown.²¹ In the DURATION-1 study, exenatide qwk was compared to bid and antibodies were more frequently observed in the exenatide qwk compared to bid.¹² No higher predictive value of individual HbA1c change in the group with increased antibody titers was shown.¹² In fact, the reduction in HbA1c was greater in exenatide qwk group with -1.9% (standard error (SE) 0.1) compared to -1.5% (SE 0.1) in the exenatide bid-treated patients.¹²

On the other hand, in the DURATION-3 study in which exenatide qwk was compared to insulin glargine, a reduced mean reduction in HbA1c in the antibody-positive group of -1.3% (SE 0.1) versus a mean reduction in the antibody-negative group of -1.6% (SE 0.1) was assessed.²² Also, Faludi et al showed that even though re-exposure with exenatide did not increase antibody formation or incidence of adverse events, positive antibody titers were associated with impaired efficacy in reducing HbA1c.²³ Studies with another GLP-1 receptor agonist taspoglutide were aborted because of increased events of hypersensitivity.⁴ Their occurrence was higher than expected.⁴ Although uncommon with an incidence of <1%, it was potentially associated with antidrug antibody formation.⁴ This was confirmed in a recent study where taspoglutide elicited more hypersensitivity and allergic disorders than

exenatide, and anti-taspoglutide antibodies occurred significantly more frequent compared to anti-exenatide antibodies.²⁴

We report a rare case of a systemic hypersensitivity reaction to exenatide (Bydureon). The reaction described above appeared after the second injection and reappeared more profoundly after the third application of the drug. The time between administration of exenatide and the reaction were few hours. Thus, a temporal coherence existed. Symptoms resolved after administration of antiallergic medication and did not reappear after discontinuation of exenatide. No alternative cause for the above-described symptoms was detected according to the patient history, so a conclusive differential diagnosis was missing. The drug was not administered again as after the positive skin tests the risk for another hypersensitivity reaction was considered to be too high. In the skin tests there was a positive reaction to both substances containing exenatide, while liraglutide was negative. The more pronounced reaction to exenatide bid (Byetta) may be explained by the different drug formulation in comparison to exenatide qwk (Bydureon).

Furthermore, as described above, a consistent biological explanation exists as the administration of GLP-1 receptor agonists has been shown to be associated with antibody formation, and GLP-1 inhibitors can prolong actions of certain neuropeptides and chemokines that may increase the possibility of an allergic reaction. While most studies did not report an effect on efficacy and safety,¹⁵ some reports did assess a possible effect on both efficacy, such as a reduction in HbA1c improvement,²² and safety, such as hypersensitivity,⁴ in GLP-1 agonists.

We therefore consider the above-described case to be a probable adverse drug reaction to exenatide according to the adverse drug reaction probability scale described by Naranjo,²⁵ with a score of 8 out of 13.

Conclusion

Considering emerging use of GLP-1 receptor agonists in this new drug class, short- and long-term risks connected with incretin treatment should be recognized. Systemic hypersensitivity reactions were rare in the early phase studies, despite the high rate of anti-exenatide antibodies. Our case, however, demonstrates that the putative formation of IgE antibodies to exenatide may be associated with hypersensitivity and thus may lead to potentially serious adverse reactions. With increasing numbers of patients treated with GLP-1 receptor agonists and self-administration outside of medical facilities, treating doctors and patients should be instructed accordingly. Severe adverse events should be reported as part of postmarketing safety surveillance to the appropriate pharmacovigilance organization.

Declaration of conflicting interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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