CASE REPORT

Linagliptin-associated blistering and ulceration

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SUMMARY

We present the case of 60-year-old man with type 2 diabetes who developed blistering after two sequential exposures to linagliptin. Linagliptin is one of the dipeptidyl peptidase 4 (DPP-4) inhibitors, a group of oral hypoglycaemic agents used commonly for the treatment of type 2 diabetes. On the first exposure to linagliptin, he developed blisters on the hands which resolved after stopping the drug. After repeat exposure, he developed two large blisters on the left foot, which burst giving rise to secondary infection, requiring hospital admission for treatment. We discuss the latest research linking DPP-4 inhibitors with adverse skin reactions and the effect of ulcers on the morbidity and mortality of patients with diabetes. This case report highlights skin reactions as an important, rare and lesser known side effect of DPP-4 inhibitors.

BACKGROUND

This case report contributes to the emerging body of evidence linking adverse skin reactions to dipeptidyl peptidase 4 (DPP-4) inhibitor use. The few existing reported cases mainly involve sitagliptin. The patient we describe was using Linagliptin when he developed two large foot blisters, which became infected, leading to cellulitis and required treatment with intravenous antibiotics. Linagliptin is part of the dipeptidyl peptidase 4 (DPP-4) inhibitor class, an oral hypoglycaemic agent used in the treatment of type 2 diabetes. Linagliptin and other DPP-4 inhibitors are widely used due to their favourable side-effect profile. However, this case highlights a rare and potentially serious consequence of DPP-4 inhibitor use.

CASE PRESENTATION

A 60-year-old man with a background of type 2 diabetes mellitus, peripheral neuropathy and no previous history of foot ulceration was prescribed linagliptin 5 mg once daily by his general practitioner (GP), in addition to his usual diabetes medications (metformin slow release 1 g twice daily and gliclazide 80 mg once daily). Three weeks later, small, painless, fluid-filled vesicles appeared first on the right hand and then, within a week, on the left hand, affecting the index and middle fingers on each hand. The patient himself stopped linagliptin without informing his GP as he was concerned that the blisters may be a side effect of the drug. Within a week of discontinuing linagliptin, the blisters resolved. However, 6 months later, his GP, either unaware (or sceptical) of the previous possible skin reaction, reinitiated linagliptin 5 mg once daily as

glycaemic control was suboptimal. The doses of metformin and gliclazide remained unaltered. Three weeks after restarting linagliptin, he developed two large blisters on the sole of his left foot. One week after the blisters formed, they burst and became infected with a purulent discharge and cellulitis then developed. At this point, he was started on oral flucloxacillin by his GP but was admitted 2 days later due to a further deterioration.

He presented to accident and emergency department in significant pain with an erythematous, swollen left foot. On examination, he had two large infected ulcers on the plantar aspect, with evidence of cellulitis extending over the dorsolateral aspect of the left foot (figure 1). There was no history of blister or bulla formation in the past apart from these two occasions outlined above. At presentation, there were no blisters or bullae present on the feet or elsewhere. There was however, evidence of two deroofed blisters forming ulcer craters on the sole of the foot. His vital signs were stable and he was afebrile.

INVESTIGATIONS

His blood results revealed an elevated C reactive protein and white cell count (table 1). He had poorly controlled diabetes (laboratory glucose 31.6 mmol/L, glycated haemoglobin 118 mmol/mol and serum osmolality 295 mOsm/kg, no ketonuria). An X-ray and MRI scan showed no evidence of osteomyelitis. A wound swab grew *Pseudomonas*, *Streptococcus* and *Acinetobacter* (table 1).

TREATMENT

He initially was commenced on an insulin infusion and linagliptin was stopped. He was treated with intravenous tazocin and teicoplanin for 6 days until cellulitis had resolved and osteomyelitis was excluded. The day after admission, intravenous insulin was stopped and he was switched back to oral hypoglycaemics—Metformin MR 1g twice daily was continued unchanged and gliclazide was titrated up to the maximum dose 160 mg twice daily. While an inpatient, he achieved acceptable glycaemic control, with capillary glucoses 7.8–11.6 mmol/L.

OUTCOME AND FOLLOW-UP

During the first 5 days of the admission, there was rapid clinical improvement, with resolution of cellulitis, reduced pain and swelling. Osteomyelitis of the left foot was excluded on both X-ray and subsequent MRI scanning. He was discharged on a 2-week course of oral clindamycin 300 mg four

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Figure 1 Patient's left foot on presentation.

times daily. He was given an air cast boot to offload the left foot and district nurses changed his dressings every 48 hours (Cavilon spray applied to ulcer base, Aquacel AG primary dressing, secured with felt and crepe bandages). There was steady improvement over the next 3 months with complete healing of the superficial ulceration (figure 2), and he was discharged from the diabetic foot clinic 3 months after his hospital admission.

DISCUSSION

Linagliptin is a DPP-4 inhibitor, part of a group of oral hypoglycaemic agents used in the treatment of type 2 diabetes that stimulates the release of insulin and decreases levels of glucagon when the portal venous glucose level is elevated. It works by competitively inhibiting the enzyme DPP-4, which degrades glucagon-like peptide 1 (GLP-1) and glucose-dependent

Figure 2 Patient's left foot 3 months after treatment.

insulinotropic polypeptide (GIP). GLP-1 and GIP are both incretins, which increase insulin synthesis and secretion from the pancreas postprandially.¹

Although this class of drugs is generally very well tolerated, rarely dermatological side effects can occur. DPP-4 is present in other parts of the body including the skin and inhibiting it can have wide-ranging effects beyond those on the pancreas.² Since their release on the market in 2006, sporadic cases have emerged supporting an association between DPP-4 inhibitors and adverse skin reactions.³ Sitagliptin in particular has been associated with Stevens-Johnson syndrome, toxic epidermal necrolysis and various 'bullous, desquamative, blistering, exfoliative, urticarial or exanthematous reactions',⁴ with about 10 identified cases of bullous pemphigoid.⁵ Vildagliptin's Food and Drug Administration approval was suspended due to preclinical trials showing it induced necrotic skin lesions in monkeys.⁶ Research suggests that adverse skin reactions are likely to occur within the first 3 months of taking the drug and as quickly as after the first dose.⁴

Case reports on linagliptin are much more limited. Haber has published two case reports of linagliptin-associated bullous pemphigoid.⁵ The mechanism is not entirely known, but is thought to be immune modulated. In particular, it could be caused by the activation of eosinophils, major contributors to blister formation, via an exotoxin-mediated mechanism.⁶ The UK Yellow Card scheme reports 68 incidents of adverse skin reactions reported for linagliptin to date, only 4 of which were classified as 'blisters', including this patient.⁷

Table 1

Medications on admission	Blood results on admission	Microbiology—wound swab
Metformin 1 g twice daily	White cell count $13.8 \times 10^9/L$	++ <i>Acinetobacter species</i>
Gliclazide 80 mg once daily	C reactive protein 58 mg/L	+++ <i>Pseudomonas aeruginosa</i>
Atorvastatin 40 mg once daily	Urea 5.8 mmol/L	(tazocin and gentamicin sensitive)
Losartan 100 mg once daily	Creatine 84 $\mu\text{mol/L}$	+++ <i>Streptococcus viridans</i>
Amlodipine 10 mg once daily	Glucose 31.6 mmol/L	
Aspirin 75 mg once daily	Haemoglobin A1c 118 mmol/mol	

Given the history of blisters after initial linagliptin use, resolving with withdrawal and then appearing again on rechallenge with the drug, skin blistering can be classified as a 'probable adverse drug reaction' with a score of 6 on the Naranjo Classification (the presence of other risk factors, namely diabetic peripheral neuropathy reduces the score from 7 to 6, but it remains a probable adverse reaction).⁸ Although a skin biopsy may have provided objective evidence (and clarified the differential diagnosis of bullous pemphigoid), the fact that the blisters had burst 3 days prior to admission and the presence of infection led us to the conclusion that the risks of carrying out a biopsy in an infected foot outweighed the benefits of obtaining histology. The patient was not referred to a dermatologist, as a clinical decision had been made to declare an adverse drug reaction and there was no history of blistering, eczema or other skin conditions prior to exposure to DPP-4 inhibitors. The main differential diagnosis would be blistering secondary to diabetic neuropathy and friction: both blisters were on the plantar aspect of the foot in weight-bearing regions—while this cannot be fully excluded the lack of a history of neuropathic blisters/ulcers before and since makes this unlikely.

The implications of developing blisters, and then ulcers, in diabetic patients are wide ranging, both for morbidity and

mortality. Patients with diabetes have impaired healing capabilities due to a combination of impaired blood supply, neuropathic changes and continued trauma, as well as increased susceptibility to infection.⁹ Research indicates that 75%–85% of leg amputations are preceded by foot ulcers.¹⁰ Furthermore, there are extensive costs associated with diabetic foot disease. In 2005, the estimated annual cost of diabetic foot complications (excluding amputation) in the UK was £252 million.¹⁰

When considering the prescription of any drug, a clinician has to weigh up the benefits against the side effect profile. DPP-4 inhibitors offer many advantages, such as a low risk of hypoglycaemia and a neutral weight profile. However, it is important that prescribers in primary and secondary care, as well as patients starting DPP-4 inhibitors, are aware to stop these drugs if they develop unexplained blisters or a rash.

Competing interests None declared.

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Learning points

- ▶ Dipeptidyl peptidase 4 (DPP-4) is present in other parts of the body including the skin and inhibiting it can have wide-ranging effects beyond those on the pancreas.
- ▶ DPP-4 inhibitors have been associated with adverse skin reactions, including blistering, Stevens-Johnson syndrome and toxic epidermal necrolysis.
- ▶ Due to propensity of patients with diabetes to develop ulcers, adverse skin reactions caused by DPP-4 inhibitors may be under-reported.
- ▶ In a patient who develops skin blistering while on a DPP-4 inhibitor, clinicians should consider whether there is a link with the medication and whether they should select an alternative agent.

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