

ORIGINAL ARTICLE

Allergic contact dermatitis caused by isobornyl acrylate in the Enlite glucose sensor and the Paradigm MiniMed Quick-set insulin infusion set

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Abstract

Background: The FreeStyle Libre glucose sensor has caused many cases of allergic contact dermatitis, and isobornyl acrylate (IBOA) in this sensor has been identified as one of the culprit allergens.

Objectives: To report on the presence of IBOA in devices produced by Medtronic, namely, Enlite sensor and insulin infusion set Paradigm MiniMed Quick-set.

Patients and Methods: Five patients reacting to the glucose sensor Enlite and/or the insulin infusion set Paradigm MiniMed Quick-set observed in three clinics (two Belgian and one Swedish) were patch tested with the baseline and other series, as well as with IBOA; four of them also with pieces of adhesive patches from the devices, and two with a thin layer chromatogram of Enlite glucose sensor extracts. Gas chromatography-mass spectrometry (GC-MS) analyses were performed.

Results: Four patients reacted to IBOA and one to colophonium, a known allergen in Enlite, and three to the adhesive part of the sensor or the insulin infusion set. IBOA was identified in the sensor by GC-MS, and its presence was indicated in the infusion set.

Conclusions: IBOA is a contact allergen in Enlite glucose sensor, and likely also in the infusion set. Therefore, these devices are not suitable alternatives for patients sensitized to the FreeStyle Libre sensor.

KEYWORDS

acrylates, allergic contact dermatitis, delayed hypersensitivity, glucose sensor, insulin pump, isobornyl acrylate, medical device

1 | INTRODUCTION

Several cases of allergic contact dermatitis (ACD) to the glucose sensor FreeStyle Libre (Abbott Diabetes Care, Witney, Oxfordshire, UK) have been described,^{1–5} demonstrating isobornyl acrylate (IBOA) as a major culprit allergen.^{1,2} We here report on five cases of ACD

resulting from the use of two other glucose sensors for patients with diabetes, namely, Enlite (Medtronic MiniMed, Northridge, California) and/or the insulin infusion set Paradigm MiniMed Quick-set (Medtronic, Minneapolis, Minnesota), the latter frequently associated with the insulin pump MiniMed 640G (Medtronic MiniMed).

2 | PATIENTS AND METHODS

2.1 | Patients

Case 1: A 46-year-old woman, working as a veterinary surgeon and suffering from diabetes mellitus type 1, had previously monitored her glycemia with the FreeStyle Libre sensor. However, because of a skin reaction 6 months following its use and ineffective protection by the use of a thin hydrocolloid dressing between the sensor and her skin, she started to use the glucose sensor Enlite and Guardian Connect Transmitter (Medtronic). After 3 weeks of use, she again developed an eczematous dermatitis at the contact sites on her arm (Figure 1).

Case 2: A 13-year-old girl with diabetes mellitus type 1 wearing a FreeStyle Libre glucose sensor and an insulin pump MiniMed 640G (Medtronic), with the Paradigm MiniMed Quick-set insulin set, developed, after 5 months of use, annular dermatitis under the adhesive patch of both devices. Patch testing demonstrated contact allergy to IBOA, and the recommendation was to avoid FreeStyle Libre and to use another glucose sensor device, namely, the Enlite sensor. Unfortunately, 3 days later the patient developed an erythematous and vesicular rash under the sensor adhesive.

Case 3: A 4-year-old girl with diabetes type 1 wearing a FreeStyle Libre glucose sensor and an insulin pump Enlite 640G (Medtronic), with the Paradigm MiniMed Sure-T insulin set, after 10 months of use developed annular dermatitis under the adhesive patch of both devices. She also developed a skin eruption 2 days after attempts to use the Paradigm MiniMed Quick-set insulin set (Figure 2).

Case 4: A 41-year-old woman with diabetes type 1, a social nurse, presented 8 months after the first application of the glucose sensor Enlite with a dermatitis at the contact site of her arm. She had never worn the FreeStyle Libre sensor.

Case 5: A 16-year-old non-atopic male with type 1 diabetes since 2012 started developing eczematous skin reactions under the FreeStyle Libre sensor 9 months following its first use. The skin reactions became

more intense and he was referred to the dermatology department where patch testing was performed. He started using the MiniMed 640G insulin pump with an infusion set (exact name unknown) and the Enlite glucose sensor, which are wirelessly connected to each other. After the first week of use, he developed an eczematous reaction under the sensor (Figure 3), less severe though than following FreeStyle Libre use, allowing him to continue using the sensor by treating the skin with a mometasone furoate spray (NASONEX; MSD, Kenilworth, New Jersey) before application, and clobetasol propionate cream (DERMOVATE; GlaxoSmithKline, Brentford, UK) after removal of the sensor. He experienced no skin reactions to the infusion set.

2.2 | Patch tests

Cases 1-3 were patch tested at the Department of Dermatology of Cliniques universitaires Saint-Luc in Brussels, Belgium; case 4 at the Department of Dermatology of the University Hospitals in Leuven; and case 5 at the Department of Dermatology, Blekinge Hospital, Karlskrona, Sweden. In Brussels, the patients were patch tested with the European Baseline Series; an acrylate, a fragrance, and a plastic and glue series (Chemotechnique Diagnostics, Vellinge, Sweden; and TROLAB, Almirall/Hermal, Reinbek, Germany); and with IBOA (Sigma-Aldrich, Steinheim, Germany), diluted to 0.1% in petrolatum (pet.) by the hospital pharmacy (Saint-Luc, Brussels, Belgium). Patch tests were applied with IQ Ultra tests chambers (Chemotechnique Diagnostics) and fixed with Fixomull stretch (BSN Medical, Hamburg, Germany) on the upper back. In Leuven, patch tests were performed with the European Baseline and an acrylate series (Chemotechnique Diagnostics) and also with IBOA 0.1% pet. using the raw material obtained from Kowa Europe (Düsseldorf, Germany). Patch tests were applied with IQ Ultra tests chambers (Chemotechnique Diagnostics) and fixed with Mefix (Mölnlycke, Göteborg, Sweden). In Karlskrona, the patient was patch tested with the Swedish Baseline Series (Chemotechnique Diagnostics)



FIGURE 1 Allergic contact dermatitis caused by the glucose sensor Enlite in patient 1

FIGURE 2 Allergic contact dermatitis caused by Paradigm Quick-set insulin set in patient 3



FIGURE 3 Allergic contact dermatitis caused by glucose sensor Enlite in patient 5

and IBOA (Sigma-Aldrich) 0.1% and 0.01% pet. Patch tests were applied with IQ Ultra tests chambers (Chemotechnique Diagnostics).

Moreover, in cases 1-4 a piece of the adhesive patch of the glucose sensor Enlite, and in cases 1-3 a piece of the adhesive patch of FreeStyle Libre as well was tested, respectively; case 5 was tested with an ultrasonic bath extract of an adhesive patch from the latter sensor. Patient 3 was tested with a piece of the adhesive patch of the Paradigm MiniMed Quick-set infusion set. The occlusion time was 2 days, and readings were performed in Brussels and Leuven on day (D) 2 and D4, and on D4 and D7 in

Karlskrona. The patch test reactions were classified according to ESCD criteria.^{1,2}

2.3 | Chemical investigations

Two Enlite sensors (LOT no. A147P) were disassembled and separate acetone extracts were prepared from the adhesive patches and the sensors (including the spots of glue that fixed the patches to the sensors). The materials of the sensor were cut into small pieces, which were extracted at room temperature in 8 mL acetone for 4 hours. The extracts were filtered and concentrated to a volume of approximately 0.3 mL. Further analyses were performed on materials from another Enlite sensor (LOT no. J055P). Here, three separate acetone extracts were made from (a) the adhesive patch, (b) the sensor itself, and (c) the glue spots removed from the bottom of the sensor. These extracts were prepared as described earlier and were evaporated to a volume of 0.1 mL. A Paradigm MiniMed Quick-set (LOT no. 02209928) unit was also disassembled and separate ethanol extracts were made from the adhesive patch and the plastic material holding the tubular catheter. Only the plastic material was cut into small pieces. These plastic material pieces and the adhesive patch were extracted in 4 and 7 mL ethanol, respectively, for 4 hours. The extracts were filtered and concentrated to a volume of approximately 0.1 mL.

All extracts were prepared and then analyzed by gas chromatography-mass spectrometry (GC-MS) at Department of Occupational and Environmental Dermatology, Skåne University Hospital in Malmö.⁶ The National Institute of Standards and Technology (Gaithersburg, Maryland) library of mass spectra was used for identification of substances. Dilutions of IBOA in acetone were used as reference standards. The detection limit of IBOA was estimated to be 0.01 mg/mL.

2.4 | Thin layer chromatography patch testing

The extracts prepared of the two Enlite sensors (with the adhesive patches removed) were used for thin layer chromatography (TLC)

patch testing.¹ TLC was performed on TLC Silica gel 60 F₂₅₄ plastic sheets (Merck, Darmstadt, Germany). Several applications of 20 µL of the extract were made next to each other on the same TLC sheet. The samples were developed with a mobile phase consisting of 70% (vol/vol) heptane (Merck) and 30% (vol/vol) ethyl acetate (VWR International, Fontenay-sous-Bois, France). The TLC sheets were allowed to dry and were then inspected under UV light at 254 and 366 nm. Spots visible under UV light were marked on the TLC sheet with a pencil. Thereafter, the TLC sheets were cut into strips to be used for patch testing. One strip of each chromatogram was used as a template when reading the test, and one strip was left to be used for chemical investigations of areas giving positive test reactions.

Two patients (patients 1 and 3) were tested with the TLC strips of the Enlite sensor. Two other patients, sensitized to the FreeStyle Libre sensor but never exposed to the Enlite sensor, were tested with the TLC strips of the FreeStyle Libre sensor. The silica gel from the areas corresponding to the site on the TLC strip giving a positive reaction was scraped off and extracted in a small volume of acetone (~0.2 mL). The extracts were then filtered and analyzed by GC-MS.

3 | RESULTS

3.1 | Patch tests

All relevant results are summarized in Table 1. Four patients reacted to IBOA 0.1% and three out of four showed a positive reaction to the adhesive part of the glucose sensor Enlite. The only patient tested with a piece of the infusion set showed a positive reaction (++) to it. Patient 4 reacted to colophonium and glyceryl rosinat, but was negative to IBOA.

3.2 | Chemical analysis

In the extract of two Enlite sensors (with the adhesive patches removed), IBOA was found in a concentration corresponding to 10 µg/sensor. No IBOA (<1 µg/patch) could be demonstrated in the extract of the two adhesive patches. In the separate extracts of the glue spots and the sensor prepared from a sensor from another batch, IBOA was found in both extracts at a concentration corresponding to an amount of 4 µg in the glue spots and 40 µg in the sensor. Again,

TABLE 1 Demographic data and patch tests results for five patients who used Enlite glucose sensor, MiniMed insulin pump, or Paradigm insulin pump produced by Medtronic

Patient	Age (y)	Sex	Centre	Devices causing ACD	Baseline series (D2/D4)	Additional patch tests (D2/D4)	IBOA 0.1% (D2/D4)	Piece of adhesive part of device			
								FreeStyle Libre	Enlite sensor	Paradigm MiniMed Sure-T insulin set	TLC Strip Enlite sensor (D2/D4)
1	46	F	UCL	FreeStyle sensor Enlite Glucose sensor	Ni +++ FM I ++ FM II +++ HICC +++	MA series: negative P&G: negative	+++	+/+	+/+	NT	-/-
2	13	F	UCL	FreeStyle sensor Paradigm MiniMed Quick-set insulin set Enlite sensor	MP -/+ SLM +++ TP ++ FM I ++ PG ++ Compositae mix II +++ BIT +/-	MA series: negative P&G: negative Epoxy resin: cycloaliphatic ++	+++	+++	-/-	NT	NT
3	4	F	UCL	FreeStyle sensor Paradigm MiniMed Sure-T insulin set	NT	MA series: negative P&G: negative	+/+	+/+	?+/+	+++	+/+
4	41	F	LEU	Enlite sensor	Colophonium +/- Ni -/+ HICC -/+ Linalool HP +/-	Glyceryl rosinat -/+	-/-	NT	+	NT	NT
5	16	M	KKA	FreeStyle sensor Enlite sensor	Thiuram mix +++ SLM +++	IBOA 0.01% ++ + (read on D4 and D7)	+++	+++ extract	NT	NT	NT

Abbreviations: ACD, allergic contact dermatitis; BIT, benzisothiazolinone; F, female; FM I, fragrance mix I; FM II, fragrance mix II; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; HP, hydroperoxides; IBOA, isobornyl acrylate; KKA, Department of Dermatology, Hospital Karlskrona; LEU, Department of Dermatology, University Hospitals KU Leuven; MA, methacrylate; MP, *Myroxylon pereirae* resin; Ni, Nickel; NT, not tested; P&G, plastic & glue series; PG, propylene glycol; SLM, sesquiterpene lactone mix; TP, tixocortol pivalate; UCL, Department of Dermatology, Cliniques universitaires Saint-Luc; -, negative; ?+, doubtful; + to +++, positive patch test reaction.

the presence of IBOA could not be demonstrated in the extract of the adhesive patch from this sensor.

The analyses of all extracts prepared from different parts of the Enlite sensor indicated the presence of hydroxycyclohexyl phenyl ketone and methyl dehydroabietate (indicated from library spectra). Furthermore, these analyses indicated the presence of *N,N*-dimethylacrylamide (DMAA) in the extracts of the sensors.

The analysis of the plastic part of the Paradigm MiniMed Quick-set infusion set demonstrated the likely presence of small amounts of IBOA (<1 µg) with the main mass fragments of IBOA observed at the expected retention time. No signs of IBOA were seen in the extract of the adhesive patch. Moreover, in the extracts of the Paradigm Quick-set presence of hydroxycyclohexyl phenyl ketone was indicated.

3.3 | Thin layer chromatography

Seven spots could be observed under UV light on the TLC strips of the adhesive patch from Enlite. One of the two patients tested with the TLC strip (Table 1) reacted to an area on the TLC with an *R_f* value $\approx$ 0.6 that was not visible to the naked eye nor observed under UV light (between spots 6 and 7; Figure 4). Two other patients, sensitized to the FreeStyle glucose sensor, also presented with a positive reaction to the same spot on the TLC strip of the Enlite extract. When material from this area was

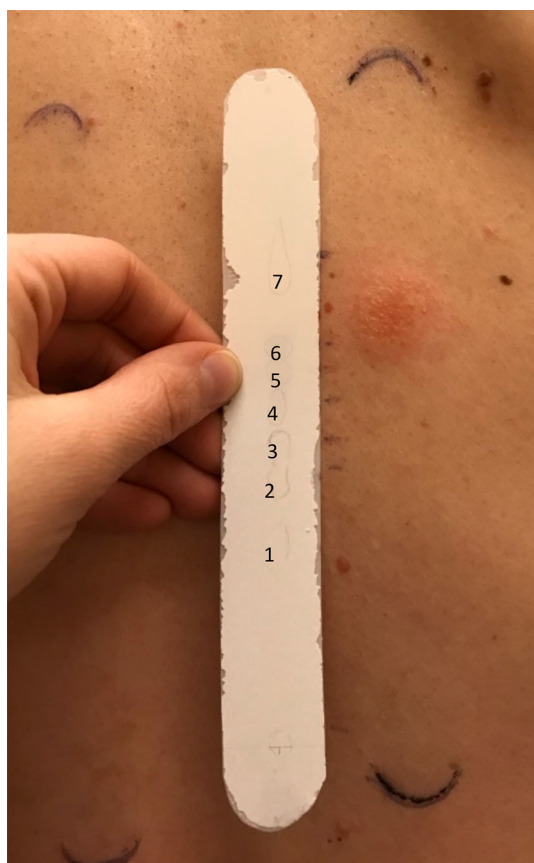


FIGURE 4 Day 4 reading of positive reaction (++) observed with a thin layer chromatography strip (Enlite sensor) in patient 3

analyzed by GC-MS, IBOA could be identified. No other substance was observed in the extract from the positive spot.

4 | DISCUSSION

The glucose sensor Enlite is a medical device developed as a continuous glucose monitoring system for patients with diabetes. This device may be worn on the skin for 6 days. It consists of a catheter with adhesive film and two transmitters. The first transmitter, the Guardian Connect (Medtronic) transmitter, which is reusable and rechargeable, is connected to the glucose sensor Enlite and sends data to the reader (often a mobile phone). The second transmitter, the Guardian 2 Link, is connected to the Enlite sensor and sends blood glucose information to an insulin pump (MiniMed 640G, Medtronic). This insulin pump is connected to the skin with an infusion set, that is, Paradigm MiniMed Quick-set or Paradigm MiniMed Sure-T.

In recent years, cases of ACD resulting from the use of medical devices in patients with diabetes have been increasingly reported in the literature. Passanisi et al⁷ described ACD from the glucose sensor Enlite caused by colophonium, the presence of which was confirmed by the manufacturer. In our patients, only case 4 presented a positive reaction to colophonium and glyceryl rosinate (–/+), the latter being a colophonium derivative. Although our GC-MS method is not optimal for analysis of colophonium-related substances, the presence of methyl dehydroabietate (indicated from library spectra) in the extracts was likely, which indicates the use of colophonium in the device. However, the other four patients were sensitized to the allergen IBOA, an allergen that was the culprit allergen in the FreeStyle Libre glucose sensor¹ and also in the insulin patch pump Omnipod,⁸ and now also detected by GC-MS analysis in the Enlite glucose sensor, and likely also in the Paradigm infusion sets. It should be noted that IBOA was also detected in insulin pump infusion sets in 1995.^{8,9} Our analyses demonstrated the presence of IBOA in the extracts of the Enlite sensors (with the adhesive patches removed) but not in the extracts of the adhesive patches. However, it is likely that small amounts of IBOA are present also in the adhesive patches (insufficient to be detected by chemical analysis), especially because three of the patients reacted to the adhesive patches tested “as is.”

Both the Enlite sensor and the Paradigm infusion set appear to also contain the photo-initiator hydroxycyclohexyl phenyl ketone, although this was not confirmed by analysis of reference sample of the substance. This may imply that adhesives based on UV-curing acrylate have been used. Furthermore, in the extracts of the Enlite sensor there was an indication for the presence of DMAA (after comparison to a DMAA reference sample), which has been previously shown to be an additional culprit allergen in FreeStyle Libre.¹⁰ However, none of the patients reported here was tested with DMAA. TLC patch testing with an Enlite sensor extract was performed to investigate whether the patients reacting to their Enlite sensors were sensitized to substances other than IBOA. However, the patient with a positive TLC patch test reacted to only one area on the TLC strip, which was subsequently demonstrated to contain IBOA.

Four of the five patients had previously worn a FreeStyle sensor before wearing the Enlite glucose sensor or insulin infusion set; therefore, primary sensitization to IBOA from the former was suspected. The exposure time for the FreeStyle Libre sensor is much longer and the concentration of IBOA in it appears to be higher compared with the Enlite sensor or insulin infusion set.¹¹ Patient 4 who reacted to colophonium (and the derivative glyceryl rosinate) but not to IBOA had never used a Freestyle sensor. Therefore, she was most likely primarily sensitized to colophonium related to/in the Enlite sensor as she had no history of colophonium hypersensitivity before starting to use the Enlite sensor, and her dermatitis appeared first after having used this sensor for 8 months. Interestingly, two of three patients with IBOA allergy and tested with a baseline series showed a simultaneous contact allergy to sesquiterpene lactone mix.¹ This surprising association has been discussed separately, a common precursor being possibly implicated.

The company concerned was contacted several times, but they never responded as to the presence of IBOA in their devices, which again highlights their unwillingness to cooperate. Due to the increasing number of ACD resulting from medical devices in patients with diabetes reported in the literature, as well as to facilitate the complex management in the follow-up of such patients, it is of utmost importance to decide, at the level of European legislation, on the obligation to provide the complete composition of medical devices.

5 | CONCLUSION

IBOA (CAS no. 5888-33-5), a known allergen in the glucose sensor FreeStyle Libre, has again been identified, both by patch tests and by chemical analyses, as the cause of ACD in four of five patients exposed to two other medical devices, namely, Enlite glucose sensor and Paradigm MiniMed Quick-set insulin infusion set. The fifth patient reacted to colophonium, an additional allergen recently identified in the Enlite glucose sensor. Therefore, these medical devices cannot be offered as alternatives for patients previously sensitized to IBOA, nor can the Enlite sensor for patients contact allergic to colophonium (and derivatives).

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CONFLICT OF INTERESTS

None to declare.

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