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 several cases of allergic contact dermatitis, and isobornyl acrylate (IBOA) was identified as one of the culprit allergens in it.

Objectives: To report on the presence of IBOA in devices produced by Medtronic, i.e., 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, one Swedish) were patch tested with a baseline and other series, as well as with IBOA; four of them also to pieces of adhesive patches from the devices, and two with a thin layer chromatogram of Enlite® glucose sensor extracts. Gas chromatography-mass spectrometry 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 by GC-MS in the sensor, and its presence was indicated in the infusion set.

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

Introduction

Several cases of allergic contact dermatitis (ACD) have been described with the glucose sensor FreeStyle® Libre (Abbott Diabetes Care, Witney, Oxfordshire, UK)(1-5), demonstrating isobornyl acrylate (IBOA) as a major culprit allergen (1, 2). We here report about five cases due to another glucose sensor for diabetes patients, i.e., Enlite® (Medtronic Minimed, Northridge, CA, USA) and/or the insulin infusion set Paradigm® MiniMed Quick-Set® **(**Medtronic, Minneapolis, Minnesota), the latter frequently associated with the insulin pump, i.e., MiniMed ® 640G (Medtronic Minimed).

Patients and methods

Patients

Case 1:

A 46-year-old woman, working as a veterinary and suffering from diabetes mellitus type 1, had previously monitored her glycaemia with 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 apply the glucose sensor Enlite® and Guardian® Connect Transmitter (Medtronic, Minneapolis, Minnesota). After 3 weeks of use, she again developed an eczematous dermatitis at the contact sites on her arm (**Fig. 1**).

Case 2:

A 13-year-old girl with diabetes mellitus type 1 wearing a FreeStyle® Libre glucose sensor and an insulin pump Minimed 640 G® (Medtronic), with the Paradigm® MiniMed Quick-Set® insulin set, developed, after 5 months of use, an 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, i.e., 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 Medtronic Enlite 640G®, with the Paradigm® MiniMed Sure-T® insulin set, developed after 10 months of use an annular dermatitis under the adhesive patch of both devices. She developed also a skin eruption two days after attempts to use the Paradigm® MiniMed Quick-Set® insulin set (**Fig.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 sensor 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 (**Fig. 3**), less severe though than it was with FreeStyle® Libre, allowing him to continue using the sensor by treating the skin with a mometason furoate spray (Nasonex®, MSD, Kenilworth, NJ, USA) before application, and clobetasol propionate cream (Dermovat®, GlaxoSmithKline,

Brentford, UK) after removal of the sensor. He experienced no skin reactions to the infusion set.

Patch tests

The 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, Vellinge, Sweden; and Trolab, Almirall, Hermal, Reinbek, Germany), and with IBOA, purchased from Sigma-Aldrich (Steinheim, Germany) and diluted to 0.1% in pet. by the hospital pharmacy (St Luc). Patch tests were applied with IQ Ultra® tests chambers (Chemotechnique) and fixed with Fixomull® stretch (BSN Medical, Hamburg, Germany) on the upper back.

In Leuven, patch tested were performed with the European Baseline and an acrylate series (Chemotechnique, Vellinge, Sweden), and also with IBOA 0.1% in pet. using the raw material obtained from Kowa Europe (Düsseldorf, Germany). Patch tests were applied with IQ Ultra® tests chambers (Chemotechnique) and fixed with Mefix® (Mölnlycke, Göteborg, Sweden).

In Karlskrona, the patient was patch tested with the Swedish Baseline Series (Chemotechnique), and isobornyl acrylate (Sigma-Aldrich, Steinheim, Germany) tested at 0.1 and 0.01% in pet. Patch tests were applied with IQ Ultra® tests chambers (Chemotechnique).

Moreover, in cases 1-4 a piece of the adhesive patch of the glucose sensor Enlite®, and in cases 1-3 of the FreeStyle® Libre, were 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 two days, and readings were performed in Brussels and Leuven on Days (D) 2 and 4, and on D4 and D7 in Karlskrona. The patch test reactions were classified according to ESCD criteria (1, 2).

Chemical investigations

Two Enlite® sensors (LOT n°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 n° J055P). Here, three separate acetone extracts were made from i) the adhesive patch, ii) the sensor itself, and iii) the glue spots removed from the bottom of the sensor. These extracts were prepared as described above and were evaporated to a volume of 0.1 mL. A Paradigm® MiniMed Quick-Set® (LOT n° 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, the latter and the adhesive patch were extracted in respectively 4 mL and 7 mL, ethanol for 4 hours. The extracts were filtered and concentrated to a volume of approximately 0.1 mL.

All extracts were prepared and then analysed by gas chromatography-mass spectrometry (GC-MS) at the Malmö department (6). The National Institute of Standards and Technology (Gaithersburg, MD, USA) 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 0.01 mg/ml.

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). Thin layer chromatography 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 S.A.S., 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 (patient 1 and 3) were tested with the TLC strips of the Enlite® sensor. Two other patients, sensitised to the Sensor FreeStyle® Libre but never exposed to the Enlite®, were tested with the TLC strips of the latter.

The silica gel from the areas corresponding to the site on the TLC strip giving a positive reaction were scraped off and extracted in a small volume of acetone (~0.2 mL). The extracts were then filtered and analysed by GC-MS.

Results

Patch tests

All relevant results are summarized in **Table 1**. Four patients reacted to IBOA 0,1% and 3 out of 4 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 glycerol rosinate, but was negative to IBOA.

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 made from a sensor from another batch, IBOA was found in both extracts at a concentration corresponding to an amount of 4µg in the glue spots and 40 µg in the sensor. Again, no presence of IBOA could be demonstrated in the extract of the adhesive patch from this sensor.

The analyses of all extracts made from different parts of Enlite sensors indicated the presence of hydroxycyclohexyl phenyl ketone and methyl dehydroabietate (indicated from library spectra). Furthermore, the 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 showed a 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 Quick-Set® Paradigm there was an indicated presence of hydroxycyclohexyl phenyl ketone as well.

Thin layer chromatography

Seven spots could be observed under UV light on the TLC strips of the adhesive patch Enlite. One of the two patients tested with the TLC strip (**Table 1**.) reacted to an area on the TLC with a Rf-value ≈ 0,6 that was not visible by the eye and not observed in UV light (between the spot 6 and 7) (**Fig. 4**). Two other patients, sensitized to the Freestyle® glucose sensor, presented also with a positive reaction to the same spot on the TLC strip of the Enlite extract. When material from this area was analysed by GC-MS, IBOA could be identified. No other substance was observed in the extract from the positive spot.

Discussion

The glucose sensor Enlite® is a medical device developed as a continuous glucose monitoring (CGM) system for diabetes patients. This device may be applied onto the skin during 6 days. It is composed of the catheter associated with the adhesive film adhering to the skin. Two transmitters can be associated. The Guardian Connect® (Medtronic, Minneapolis, Minnesota), 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, Minneapolis, Minnesota). This insulin pump is connected to the skin with an infusion set, i.e., Paradigm® MiniMed® Quick-set® or Paradigm® MiniMed Sure-T®.

In recent years, cases of ACD with medical devices in diabetic patients have been increasingly reported in the literature. Passanisi et al. (7) 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, there was a likely presence of methyldehydroabietate (indicated from library spectra) in the extracts, which indicates the use

of colophonium in the device. However, the other four patients were sensitised to IBOA, an allergen that was the culprit allergen in the FreeStyle® Libre glucose sensor (8) and also in the insulin patch pump OmniPod (1), and now also detected by CG-MS analysis in the Enlite® glucose sensor, and likely also in the Paradigm® infusion sets. It should be noted that IBOA had already tested positively in relation with insulin pump infusion sets in 1995 (9, 10). 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 since 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 previously has shown to be an additional culprit allergen in FreeStyle Libre® (11). However, none of the patients reported here was tested with DMAA. TLC patch testing with an Enlite sensor extract was performed in order to investigate whether the patients reacting to their Enlite sensors were sensitized to other substances than IBOA. However, the patient with a positive TLC patch test reacted to only one area on the TLC strip, which subsequently was demonstrated to contain IBOA.

Four out 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 to the Enlite® sensor or insulin infusion set (12). Patient 4 who reacted to colophonium (and the derivative glyceryl rosinate)

but not to IBOA had never used a Freestyle® sensor. She therefore most likely was 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 the dermatitis appeared first after having used this sensor for 8 months.

Interestingly, 2/3 patients with IBOA allergy and tested with a baseline series, showed a simultaneous contact allergy to sesquiterpene lactone-mix (SLM) (1). This surprising association has been discussed separately, a common precursor being possibly implicated.

The respective company was contacted several times, however, 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 from medical devices in diabetic patients reported in the literature, but also in order 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.

Conclusion

Isobornyl acrylate (CAS n°5888-33-5), a known allergen in the glucose sensor FreeStyle® Libre, has again been identified, both by patch tests and chemical analyses, as the cause of ACD in four out of five patients exposed to two other medical devices, i.e. 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).

Table 1. Demographics data and patch tests results for 5 patients caused by Enlite® glucose sensor, Minimed Insulin Pump or Insulin pump Paradigm® produced by Medtronic.

Patient	Age (years)	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			TLC Strip Enlite® sensor (D2/D4)
								FreeStyle® Libre	Enlite® sensor	MiniMed Sure-T® Paradigm® insulin set	
1	46	F	UCL	FreeStyle® sensor Enlite® Glucose sensor	Ni ++/++ FMI +/+ FMII++/++ 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+/+ FMI +/+ PG +/+ Compositae mix II ++/++ BIT +/?	MA series: negative P&G: negative Epoxy resin: resin epoxy 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 rosinate -/+	-/-	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

ACD: allergic contact dermatitis; BIT, benzisothiazolinone; F, female; FMI, Fragrance mix I; FMII, fragrance mix II; IBOA, isobornyl acrylate; KKA: Dermatology, Hospital Karlskrona; LEU, Dermatology, University Hospitals KU Leuven; MP, Myroxylon pereirae; HICC: hydroxyisohexyl cyclohexene carboxaldehyde; Ni, Nickel; NT, not tested; PG, propylene glycol; P&G: Plastic & Glue series; SLM, sesquiterpene lactones mix; TP, tixocortol pivalate; UCL, Dermatology, Cliniques universitaires Saint-Luc ; −, negative; ?+, doubtful, + to +++, positive patch-test reaction

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